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Medical and Biomedical Applications of Shock Waves

Springer

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ISSN 2197-9529 ISSN 2197-9537 (electronic)
Shock Wave and High Pressure Phenomena
ISBN 978-3-319-47568-4 ISBN 978-3-319-47570-7 (eBook)
DOI 10.1007/978-3-319-47570-7

Library of Congress Control Number: 2016954236

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

In February of 1980, the first patient was treated by a lithotripter in Munich, Germany; by March of 1984, Jim Lingeman was treating patients at Methodist Hospital in Indianapolis, and by December of that year, the US FDA had approved lithotripters for general use in the population. The phenomenal rise of this revolutionary new technology significantly changed the way the urology community approached urolithiasis and, to a certain extent, led the way for the medical community to embrace noninvasive medical procedures. In this book, Achim Loske has examined not only lithotripsy but the broad use of shock waves in current medical practice, as well as their potential applications in the future.

After a brief introduction to the topic in Chap. 1, Chap. 2 provides a detailed and very interesting historical account of the development of the lithotripter, the first broadly accepted clinical use of shock waves in medicine. Although the German physicians who first used the lithotripter in a clinic had successfully treated a number of patients, the American Urological Association rejected their abstract in its annual meeting in 1981. Nevertheless, lithotripsy was soon recognized as a much preferred option for urolithiasis. Perhaps the greatest attraction of this new technology was its simplicity, as well as the available alternative at that time, viz., a lithotomy—an invasive surgical procedure that resulted in a significant morbidity, a considerable recovery time, and not an insignificant mortality. Lithotripsy was a completely noninvasive procedure that performed the required therapeutic effect at a distance; patients were discharged soon after the procedure and experienced practically no side effects. Within a few years, at least in the USA, over 80 % of patients who could not pass their stones naturally were treated with lithotripsy. A brief description of other applications of shock waves in medicine is also given in Chap. 2.

Although this book will be of considerable interest to those who are currently performing research in the general area of shock waves in medicine, it should also be of interest, and value, to those students and young professionals who may want to enter this field of research. In particular, Chap. 3 gives a detailed introduction to the basic physics and engineering terminology, as well as the methodology needed to understand how shock waves can be used to treat a number of medical conditions.

A particular topic that is covered in some detail is how measurements can be made of intense shock waves. When such waves are propagated in water, they will often generate cavitation, which can destroy any sensor that is used to determine the shock wave parameters. A description of those hydrophones that are less susceptible to cavitation is given as well as techniques to measure the degree of cavitation itself.

If a shock wave is to generate a desirable medical effect, it is necessary to understand how these waves interact with matter, particularly kidney stones and tissue. This topic is covered in Chap. 4, starting with a brief tutorial on the properties of shock waves and their behavior, such as propagation and attenuation, reflection and refraction, diffraction, and the forces and effects that they generate when interacting with matter. One of the most important of these is cavitation, which can act as an energy concentrator. When the negative pressure intrinsic to a shock wave is propagated in water, a vapor cavity is formed which subsequently collapses and concentrates the energy used to form the cavity into a very small region of space. This energy concentration can be as high as 11 orders of magnitude. Accordingly, when a shock wave interacts with a stone, the cavitation produced can create cracks and crevices within the stone itself, which weaken the stone to stress forces that can result in fragmentation. When the shock wave propagates into the stone, shear stresses are generated within the stone, which can also result in fragmentation. Interestingly, after years of study, the relative roles of cavitation and shear stresses are still not clearly understood in stone comminution. Both are probably required for a successful procedure. A detailed account of these and other effects is given in this chapter. Furthermore, similar effects are generated in tissue, and a brief but detailed description of the mechanisms for tissue damage is also given.

The majority of effort in this book is devoted to shock wave lithotripsy, and that topic is covered extensively in Chap. 5. A description is given of the various lithotripter types, which differ mainly in the manner in which they generate shock waves. The original Dornier *HM3* used a spark source, which had its deficiencies—viz., the spark plug had to be replaced after a few thousand shocks, and shocks produced were not that repeatable. There was an evolution to piezoelectric sources and then to electromagnetic sources, which appear now to be the most favored. There was also an evolution to a much smaller focal spot, which was intended to reduce the pain experienced by the patient and also to increase the peak shock wave pressure. These small-spot lithotripters could also be used without anesthesia. Unfortunately, along with this evolution was a diminution in effectiveness. The *HM3* is still considered the gold standard of lithotripters, although there are only a few still in operation. These lithotripter types and their advantages and disadvantages are described in great detail in this chapter. There is also a thorough description of the use of lithotripters in urology, with their contraindications and reasons for their occasional ineffectiveness. Indeed, the use of lithotripters to treat urolithiasis has dropped from near 80 to near 50 % in the USA. Perhaps most important for the professional, there is an excellent description of the protocols that lead to maximum stone comminution and minimal tissue damage. For example, although there is a temptation to use higher shock wave rates to more rapidly complete a procedure, it has been shown that lower rates significantly improve stone comminution. Although most manufactures

will contend that there is insignificant tissue damage, studies with animals have shown that when used at high pulse rates and high shock wave pressures, there is considerable damage to kidney tissue, especially when multiple treatments are applied to stone reformers. In this chapter, there is also a thorough treatment of the physical mechanisms leading to stone fragmentation with a detailed description of the cavitation and shear stress mechanisms. Finally, there is a useful discussion of the "failure modes" of using lithotripsy, such as bubbles on the coupling membrane and patient movement during treatment.

Not only have shock waves been found to be the basis of the technology of shock wave lithotripsy, but they can be used in a number of ways to treat various medical conditions and pathologies. Because shock wave devices can be applied noninvasively, they have a special attraction to patients. Loske describes a large number of these applications of shock waves in Chap. 6. Among the many uses are for plantar fasciitis, bone and wound healing, aesthetic dermatology, and chronic pelvic pain syndrome. One of the most important applications is to treat heart disease. Studies have shown that if shock waves are directed toward areas of ischemia in the heart, angiogenesis and neovascularization can be generated, leading to improved heart function. Apparently, the microtrauma induced by cavitation stimulates the body's repair mechanisms, including the immune system. This is a very active area of research, and this chapter is a must-read for students interested in shock wave research.

The final chapter is devoted to anticipating the potential applications of shock waves in the future. Remarkable new discoveries lie in such areas as neurosurgery, needleless injection, bacterial transformation, and site-specific drug delivery. As described in this chapter, not only have shock waves been shown to permeabilize cells to drugs, but they can also enable genetic material to be incorporated into the nucleus, and then these cells can express the particular function of that material.

This book should serve as an important resource to those involved in research in this particular area, if not only for its over 1600 references that provide a mapping of the entire field of medical shock wave research. It can be useful also to the novice who wants to build a knowledge base in this area, as it covers all the essential physics that needs to be known to understand the topic. It also serves to show in a historical sense how medical technology evolves. Recently, the introduction of medical devices using intense sound fields in a noninvasive manner, typically called HIFU (high-intensity focused ultrasound) systems, has been approved by the US FDA to treat conditions as diverse as prostate cancer and essential tremor. These HIFU devices are simply lithotripters with longer pulses and better imaging, which certainly pays homage to the developers of early lithotripters, and the lessons learned in the evolution of this technology.

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Lawrence A. Crum

Preface

This book was written with the aim of widening the reader's spectrum of knowledge regarding the uses of shock waves in medicine and biology, as well as to contribute to safer and more efficient treatments and encourage scientific research. For experts, it may be a stimulus to generate innovative ideas and introduce their colleagues and students to novel topics. Each chapter was written to be read as smoothly as possible, without continuous interruptions to look up the meanings of specialized terms. Nevertheless, it was difficult to decide which terms should be considered as "specialized" or "not obvious" and which words are part of the cultural heritage of most academicians. Depending on his background, the reader may want to skip certain sections of this book, keeping them as a reference to look up specific data or details on published research.

Collaborations between specialists from several areas, such as physics, mathematics, biology, medicine, engineering, and chemistry, are required to develop biomedical improvements and implement experimental and clinical protocols. This need for teamwork has increased the necessity for researchers to understand concepts belonging to areas that are different from their field of expertise; however, the learning process may be difficult due to the lack of a bibliography for nonspecialists and because of the time demanded to become involved in unfamiliar topics. One of the goals of this book is to foster interactions between scientists so that, for instance, a molecular biologist may have a fruitful talk with a specialist in fluid dynamics about how to take advantage of acoustic cavitation to genetically transform tumor cells or so that a urologist and a computer engineer can analyze algorithms to predict successful outcomes in extracorporeal lithotripsy. Some sections of this book may also serve as a reference during the writing of scientific papers.

It is interesting but also worrisome that the clinical use of focused shock waves and radial pressure waves started long before the basic phenomena involved were fully understood. Evidence of this is the vast number of articles reporting in vitro and in vivo experiments published many years after the first clinical application. The underlying responsibility of the scientific community and the manufacturers of clinical equipment is evident. Further research to better understand the interactions of pressure waves with living tissue and cells will certainly lead to safer

therapies and novel biomedical uses. Worldwide, there are more research groups working on shock wave-related topics than ever, indicating that this is still a promising research field.

The biomedical applications of shock waves are fascinating. I hope that all readers will benefit from the insights provided in this book and enjoy reading it as much as I enjoyed writing it. Hopefully, many of them will be inspired to develop further improvements and enhance the understanding of the phenomena involved in the medical and biomedical applications of shock waves.

Querétaro, Qro., Mexico — Achim M. Loske
September 17th, 2016

Contents

Abbreviations

ACD	Active cavitation detection
ALA	5-Aminolevulinic acid
ALP	Alkaline phosphatase
AMI	Acute myocardial infarction
AMT	*Agrobacterium*-mediated transformation
AOFAS	American Orthopaedic Foot and Ankle Society
AP	Anteroposterior
ATCC	American Type Culture Collections
ATP	Adenosine triphosphate
AUA	American Urological Association
AVNFH	Avascular necrosis of the femoral head
AWT	Acoustic wave therapy
BIA	Bioimpedance analysis
BMC	Bone mineral content
BMD	Bone mineral density
BMES	Bone marrow edema syndrome
BMFT	*Bundesministerium für Forschung und Technologie*
BMI	Body mass index
BMP	Bone morphogenic protein
BOP	Bleeding on probing
BRM	Biological response modifiers
BTJ	Bone–tendon junction
BTX-A	Botulinum toxin type A
BWL	Burst wave lithotripsy
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAT	Computerized axial tomography
CBD	Common bile duct
CC	Craniocaudal
CCP	Chronic calcific pancreatitis
CCS	Canadian Cardiovascular Society

CFSL	Cavitation-field sonoluminescence
CFU	Colony-forming units
CGIC	Clinical global impression of change
CIRF	Clinically insignificant residual fragments
CITA	Chronic inflammation of the tunica albuginea
CMS	Constant–Murley score
CP	Cerebral palsy
CPDT	Complex physical decongestive therapy
CPPS	Chronic pelvic pain syndrome
CPSI	Chronic prostatitis symptom index
CSS	Cellulite severity scale
CSWT	Cardiac shock wave therapy
CT	Computed tomography
CTN	Computed tomography attenuation number
DECT	Dual-energy computed tomography
DESWT	Direct epicardial shock wave therapy
DFU	Diabetic foot ulcers
DIGEST	*Deutschsprachige Internationale Gesellschaft für Extrakorporale Stosswellentherapie*
DM	Diabetes mellitus
DM2	Diabetes mellitus type 2
DMEM	Dulbecco's Modified Eagle's Medium
DNA	Deoxyribonucleic acid
DPCD	Dual passive cavitation detection
EAU	European Association of Urology
ECG	Electrocardiogram
ECL	Electroconductive lithotripsy
ECM	Extracellular matrix
ED	Erectile dysfunction
EFD	Energy flux density
EHS	Erection hardness scale
ELISA	Enzyme-linked immunosorbent assay
EMDA	Electromotive drug administration
EML	Extracorporeal microexplosive lithotripsy
EMSE	Electromagnetic shock wave emitter
EPAT	Extracorporeal pulse activation therapy
EQ	Efficiency quotient
ERCP	Endoscopic retrograde cholangio-pancreatography
ERPF	Effective renal plasma flow
ERK	Extracellular signal-regulated kinase
ERK1/2	Extracellular signal-regulated kinase ½
ESWA	Extracorporeal shock wave application
ESWC	Extracorporeal shock wave chemotherapy
ESWL	Extracorporeal shock wave lithotripsy
ESWT	Extracorporeal shock wave therapy

FACS	Fluorescence-activated cell sorting
FD	Fluorescein-labeled dextran
FDA	Food and Drug Administration of the United States of America
FFI	Foot function index
FITC	Fluorescein isothiocyanate
FMP	Fat mass percentage
FOPH	Fiber-optic probe hydrophone
frESWT	Fractionated repetitive extracorporeal shock wave therapy
FRV	Functional renal volume
FWHM	Full width at half maximum
GFP	Green fluorescent protein
GFR	Glomerular filtration rate
HBOT	Hyperbaric oxygen therapy
HEK	Human embryonic kidney
HESW	High-energy shock waves
HIFU	High-intensity focused ultrasound
HMEC	Human microendothelial cells
Ho:YAG	Holmium:yttrium aluminum garnet
hPDLF	Human periodontal ligament fibroblasts
HU	Hounsfield units
HUVECs	Human umbilical vein endothelial cells
IC	Interstitial cystitis
IEC	International Electrotechnical Commission
IIEF-EF	International index of erectile function-erectile function domain
INSERM	French National Institute of Health and Medical Research
IPP	*Induratio penis plastica*
ISMST	International Society for Medical Shockwave Treatment
KT	Renal cortical thickness
KUB	Kidney, ureter, and bladder
KZK	Khokhlov–Zabolotskaya–Kuznetsov
LBP	Low-back pain
LE	Lateral epicondylitis
LI-ESWT	Low-intensity extracorporeal shock wave therapy
LiPH8	Lignin peroxidase isozyme H8
LISW	Laser-induced stress waves
LPS	Lipopolysaccharide
LSHD	Light spot hydrophone
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAPH	Magnesium ammonium phosphate hydrogen
MBSL	Multibubble sonoluminescence
MD	Molecular dynamics
MET	Medical expulsive therapy
MetS	Metabolic syndrome
MI	Myocardial infarction

MnP1	Mitochondrial nucleoid protein
MRI	Magnetic resonance imaging
MSD	Mean stone density (mean stone CT density)
MT	Muscle thickness
MTBE	Methyl tert-butyl ether
MTE	Mean transformation efficiency
NCCT	Non-contrast computed tomography
NCST	Non-calcifying supraspinatus tendinopathy
Nd:YAG	Neodymium-doped yttrium aluminum garnet
NF-kappaB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHANES	National health and nutrition examination survey
NIH	National Institute of Health
NIH-CPSI	National Institute of Health chronic prostatitis symptom index
NISWT	Noninvasive shock wave thrombolysis
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OP	Osteogenic protein
PBS	Phosphate-buffered saline
PCA	Patient-controlled analgesia
PCD	Passive cavitation detection
PCI	Percutaneous coronary intervention
PCNL	Percutaneous nephrolithotomy
PCR	Polymerase chain reaction
PD	Pancreatic duct (in Chap. 5); Peyronie's disease (in Chap. 6)
PDE5I	Phosphodiesterase type 5 inhibitor
PDE5Is	Phosphodiesterase type 5 inhibitors
PDI	Percussion, diuresis, and inversion
PDLF	Periodontal ligament fibroblasts
PDT	Photodynamic therapy
%PAP	Percentage of post-SWL auxiliary procedures
%PPAP	Pre- and post-SWL auxiliary procedures
%RT	Percentage of re-treatments
%SFP	Percentage of stone-free patients
PF	Plantar fasciitis
PGE-2	Prostaglandin E2
PGF	Placental growth factor
PGI-2	Prostaglandin I2
PII	Pulse intensity integral
pIL-12	Plasmid coding for interleukin-12
PMMA	Polymethyl methacrylate
PNL	Percutaneous nephrolithotomy
PVDF	Polyvinylidene fluoride
RCT	Randomized controlled trial
RCTs	Randomized controlled trials

rESWT	Radial extracorporeal shock wave therapy
rIL-12	Recombinant interleukin-12
RIRS	Retrograde intrarenal surgery
RNA	Ribonucleic acid
ROM	Range of motion
RPF	Renal plasma flow
RSS	Rodnan skin score
RSWT	Radial shock wave therapy
SAQ	Seattle angina questionnaire
SBOTE	Spasticity treated by botulinum toxin and extracorporeal shock wave therapy
SBSL	Single-bubble sonoluminescence
SDT	Sonodynamic therapy
SEM	Scanning electron microscopy
SFR	Stone-free rate
siRNA	Short interfering ribonucleic acid
SPECT	Single-photon emission computed tomography
SRC	Simple renal cysts
SSc	Systemic sclerosis
SSD	Skin-to-stone distance
SST	Simple shoulder test
ST	Soft-tissue thickness
STP	Standard temperature and pressure
SW	Shock waves
SWCA	Shock wave catheter ablation
SWL	Shock wave lithotripsy
TAD	Temporary anchorage device
TADs	Temporary anchorage devices
T-DNA	Transferred deoxyribonucleic acid
TM	Tooth mobility
TMR	Transmyocardial laser revascularization
TPST	Trigger point shock wave therapy
TVC	Total viable count
UPJ	Ureteropelvic junction
URS	Ureteroscopy
UV	Ultraviolet
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
YAG	Yttrium aluminum garnet

Chapter 1
Introduction

During the last 30 years, biomedical applications of shock waves have developed enormously and have been established in medicine for safe and effective treatments for several diseases. Extracorporeal shock wave lithotripsy (ESWL or SWL), i.e., the noninvasive use of shock waves to break up concrements formed inside the body, revolutionized the treatment of urolithiasis in the early 1980s and motivated considerable research. SWL to treat stones in the gallbladder, the common bile duct, the pancreatic duct, and the salivary gland ducts followed.

For many years, improvements to clinical equipment came rather slowly. Enhancements were focused on ergonomics, user convenience, automation, imaging and downsizing, rather than on the fundamental principles of the interaction between shock waves and the human body. In the meantime, basic research generated new applications of shock waves in diverse areas of medicine and biotechnology. Today, extracorporeal shock wave therapy (ESWT) and radial pressure wave therapy are helpful in an increasing variety of indications in orthopedics and traumatology, such as treatment of calcium deposits in tendons and inflammation of tendons, as well as bone and wound healing. Shock waves are also used in cardiology to treat coronary artery disease and have been proposed as a therapy for patients suffering from the growth of fibrous plaques in the penis, to alleviate chronic pelvic pain syndrome, and to treat erectile dysfunction and interstitial cystitis.

The bactericidal effects of shock waves have also been studied, and they may have uses in urology to treat chronic bacterial prostatitis, as well as in several areas of industry. Shock wave-induced noninvasive drug and gene delivery has attracted significant interest because of its potential applications in cancer treatment and gene therapy. Moreover, the recent results on shock wave-mediated genetic transformation of filamentous fungi could revolutionize many areas in biotechnology.

This book is intended for both the novice in the field and the expert. Because the biomedical applications of shock waves encompass an extensive field, most readers will be experienced in certain areas and inexperienced in others.

A brief history of the use of shock waves in medicine is given in Chap. 2, focusing mainly on the early days of SWL. Some basic definitions, mandatory to everyone working in the field, as well as the main characteristics of focused shock waves and radial pressure waves as used in biomedical applications are discussed in Chap. 3. An overview of the main physical phenomena involved when shock waves interact with matter is given in Chap. 4, including some of the biochemical effects of shock waves on living tissue. Special attention was given to shock wave-induced cavitation because it is one of the main phenomena responsible for the effects observed in SWL and ESWT, but it is also an important mechanism by which shock waves inactivate bacteria, transfect cells, and transform microorganisms. Fundamental concepts of shock wave generation and the working principles of extracorporeal lithotripters are described in the initial sections of Chap. 5, followed by treatment strategies, contraindications, and recommendations to improve SWL outcomes, including lithotripsy for gallbladder, pancreatic, common bile duct, and salivary gland stones. Readers interested in ESWT will find information on several clinical applications in Chap. 6. A few representative radial pressure wave sources are also described. Finally, the last chapter is dedicated to the use of shock waves in oncology, shock wave-mediated cell transfection, genetic transformation of microorganisms, and bactericidal effects of shock waves. Emerging therapies, such as the removal of tooth biofilm, regeneration of alveolar bone, eradication of periodontal pathogens, and reduction of tooth mobility by shock waves, as well as needleless injection are also discussed. Even if this book includes most of the latest developments and research topics, it is far from exhaustive. Scientific and technological advances occur so quickly that a book on such a vast area as the biomedical applications of shock waves can never be completely up to date.

Physicists from the shock wave community may find this book helpful to collaborate with scientists from other areas, such as medicine, molecular biology, chemistry, and neurobiology. Because misconceptions regarding shock wave physics are still common among physicians, it is the responsibility of physicists to provide practical information and explain the phenomena involved in the use of focused shock waves and radial pressure wave devices. This book may help with this purpose.

Even if suggestions for clinical uses are included, none of the sections are intended to substitute for specialized training. Training must involve thorough theoretical and practical instruction by experts in the field and should never be substituted by short courses. Good results can be obtained from most certified systems on the market, as long as they are used properly, following an adequate protocol and thorough patient selection. Furthermore, as technology is evolving quickly, some systems and methodologies described here may not correspond to the current state of the art, and it is the responsibility of the reader to update his knowledge before using shock waves or radial pressure waves in clinical practice.

In most sections, several research articles are discussed, but the book is not intended to be a review of the existing literature, as inevitably, many excellent papers are not mentioned. The selection of the articles included was not only based

on a personal evaluation of their scientific quality but also on their role in the development of shock wave research, their potential to introduce the reader to specific subjects and the availability of the information. Likewise, only a few representative samples of medical equipment could be mentioned, whereas many other excellent systems were not. For clarity, most figures are simplified drawings with false colors (*eBook*).

Hopefully, some of the possible uses of shock waves described in the last chapter will become routine clinical applications in the near future. As the understanding of the detailed phenomena involved in the interaction of shock waves with living organisms progresses, novel and probably unexpected research areas will arise, allowing the medical and biomedical applications of shock waves to continue to evolve.

Chapter 2
Brief Historical Background

It would be virtually impossible to come up with just one inventor of the first clinical application of shock waves: extracorporeal shock wave lithotripsy (SWL). As with many other technological developments, contributions came from brilliant scientists who happened to be working on the right topic at the precise moment. Regardless of conceiving ideas of a possible medical application of shock waves, it must be considered that going from laboratory experiments to a clinical prototype required a lot of self-confidence, an efficient coordination between physicists, engineers, and medical doctors, as well as a huge investment. Without a doubt, SWL revolutionized urology, and will get a place in the history of medicine as one of the most outstanding technological developments.

After demonstrating the feasibility of comminuting urinary calculi through shock waves without surgery, the next obvious step was to explore their use for treating calculi in other parts of the body. By trying to increase the efficiency of the equipment and reducing damage to affected tissues, many other applications, never thought of before appeared. Several research groups focused on the interaction between shock waves and living tissue, and started publishing results of multidisciplinary studies. In many countries, the use of shock waves to treat orthopedic-related ailments soon outscored the number of patients treated with SWL. Nowadays, biomedical applications of shock waves include such a large variety that it would be a huge project to thoroughly describe the historical development of each of them.

This chapter is a summary of the amazing development of SWL, as well as of the rising of some other clinical applications. For further information, the reader may consult the texts cited at the end of this book (Brendel 1986; Chaussy and Fuchs 1987; Jocham 1987; Lingeman et al. 1989, 2003; Delius and Brendel 1990; Haupt 1997; Lingeman 1997; Loske and Prieto 1999; Thiel 2001; Forssmann 2006; Chaussy et al. 2007; Loske 2007; Wess 2009; Dreisilker 2010b; Mittermayr et al. 2012).

The interaction of shock waves with living tissue became a topic of interest during the Second World War. Severe damage to lung tissue suffered by castaways swimming in the water when anti-submarine warfare weapons were detonated far

away was frequent (Krause 1997). Research mainly focused on how to protect the human body from shock waves and not on their beneficial uses. Interestingly, the concept of using shock waves to disintegrate calculi inside the human body is old. In the 1950s, Yutkin developed a device called *URAT-1* to comminute bladder stones using shock waves produced by electric discharges between two electrodes located at the tip of an endoscope (Loske and Prieto 1999; Wess 2009). The idea to noninvasively destroy calculi using pressure waves generated outside of the body is also old. It was conceived long before SWL was a reality. Initial trials to disintegrate concretions by means of ultrasound were performed during the 1940s. Lamport and colleagues (1950) successfully fragmented gallstones after 5–60 s exposure to continuous wave ultrasound. Similar experiments were reported by Berlinicke and Schennetten (1951), Mulvaney (1953), and Coats (1956); however, the technique did not progress, mainly because stone fragmentation was accompanied by significant tissue damage.

A system very similar to the first clinical electrohydraulic shock wave generator, patented by Hoff and Behrendt (1976) and described in Sect. 5.2.1, was proposed in the 1940s (Rieber 1947). Shock waves generated by a high-voltage electric discharge at the inner focus of an oil-filled paraellipsoidal metallic reflector were supposed to destroy brain tumors (Fig. 2.1). The device was never used clinically and many years passed until the spark-gap method was proposed once again to produce shock waves for an extracorporeal application.

During experiments with small high-speed projectiles in the early 1960s, which generated shock waves as those produced by micrometeorites and raindrops impinging on satellites and aircraft structures, engineers at the aerospace company Dornier in Friedrichshafen, Germany discovered that pain similar to an electric discharge

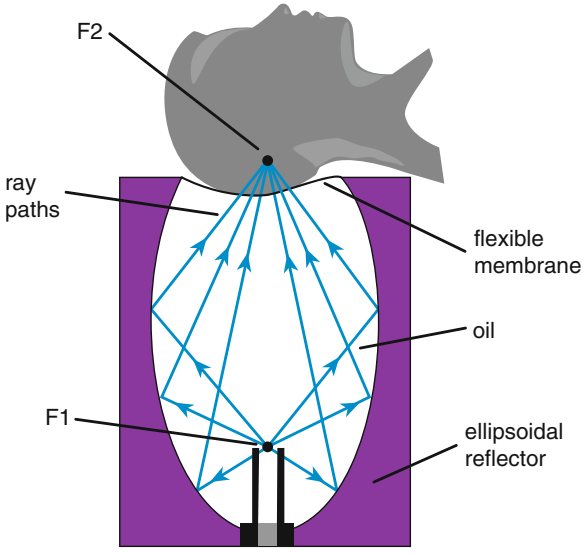


Fig. 2.1 Schematic of a spark-gap shock wave generator, patented in 1947. Analogous to modern electrohydraulic shock wave sources, an electric discharge between two electrodes placed at the first focus (*F1*) of an oil-filled paraellipsoidal reflector produces a shock wave which is reflected off the reflecting surface and focused towards the outer focus (*F2*). A flexible membrane couples the shock waves into the patient

Fig. 2.2 Photograph of Eberhard Häusler (*left*), one of the physicists that did pioneering contributions to the development of extracorporeal lithotripsy, and Francisco Larrondo, the urologist that operated the first Dornier *HM4* lithotripter in Mexico

was felt when touching the target of the experimental setup at the moment of projectile impact. Measurements revealed that this sensation was not due to electricity. The phenomenon stimulated research to better understand the effects of shock waves on living beings.

Pioneering contributions to the development of SWL were done by Eberhard Häusler (Fig. 2.2) from the Technical University of Saarbrücken, Germany (Häusler and Kiefer 1971). It seems that during a lunch at a restaurant in Meersburg, Germany, Häusler commented for the first time the possibility of using shock waves to destroy kidney stones with technicians from Dornier. Initially, the goal of the collaboration between Häusler and Dornier was to study the erosion caused by tiny raindrops on metallic structures (Fig. 2.3). Nevertheless, the idea of crushing kidney stones without surgery was so appealing that not only the physicists and engineers from Dornier, Günther Hoff, Armin Behrendt and Wolfgang Hepp, but also physicians from the University of Munich, such as the urologist Egbert Schmiedt were enthusiastic

Fig. 2.3 Photograph of a ten-penny coin of the former Federal Republic of Germany, perforated by a high-speed water drop at the High Speed Physics Laboratory of the Saarland University, Saarbrücken, Germany. The experimental arrangement was used to show that a single water drop can produce severe damage to solid structures if accelerated at supersonic speed. (Courtesy of E. Häusler)

about it (Wess 2009). In a chapter entitled "Der schwebende Patient" (The floating patient), Othmar Wess, a former employee (1979–1987) at Dornier, commented that good ideas are always simple, at least retrospectively. To perform SWL, shock waves should be generated outside the patient's body and focused on the kidney stone until it is pulverized. The fragments would be eliminated during urination. Nevertheless, the technological and medical challenges to pass from the idea to reality were immense.

Initially, kidney stones were destroyed in vitro inside a closed waveguide using shock waves produced by high-speed (up 2000 m/s) water drops (Häusler and Kiefer 1971). Shortly later, the feasibility of kidney stone destruction by shock waves was demonstrated exposing concrements in a water tank to shock waves produced with a gas gun (Fig. 2.4) (Hepp 1972). Häusler reported his initial results during a conference of the German Physical Society in 1971, leading to studies with Manfred Ziegler, a urological surgeon from the University of Saarbrücken.

A federal research project, sponsored by the West German Ministry of Research and Development, started in January 1974. Hoff and Behrendt developed the principle of generating underwater shock waves by high-voltage electric discharges at the focus of a semiellipsoidal metallic reflector (Hoff and Behrendt 1976). This shock wave source was installed in the first experimental lithotripter, called *TM1*. Christian Chaussy was a staff member at the Institute for Surgical Research of the Ludwig-Maximilian University, headed by Walter Brendel. He started his residency in Urology in 1975. During that time, Egbert Schmiedt, head of the Department of Urological Surgery of the same university, accepted the offer from Dornier to do research on the effects of shock waves on kidney stones. Christian Chaussy, the urologist Ferdinand Eisenberger, and Bernd Forssmann, a physicist at Dornier, studied the in vitro and in vivo interaction of underwater shock waves with cells and tissue (Chaussy et al. 1976, 1978, 1979b; Eisenberger et al. 1977). Chaussy created a novel model to implant human kidney stones into the renal pelvis of healthy dogs

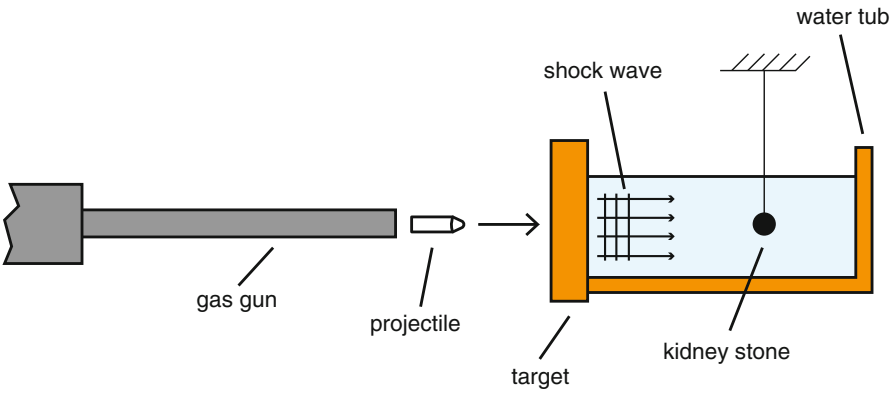


Fig. 2.4 Schematic of an experimental device used to generate underwater shock waves by the impact of a projectile on a target. Shock waves propagated through the water, destroying a kidney stone suspended inside the water tank. (Courtesy of C. Chaussy)

in order to perform the initial in vivo SWL treatments (Chaussy et al. 1979a; Chaussy and Staehler 1980). An improved shock wave source and an ultrasound *A* scanner were tested in the second extracorporeal lithotripter (*TM2*); however, ultrasound imaging did not work satisfactorily and the feasibility of the project was seriously questioned. (In the *A*- or *amplitude-mode* an ultrasound transducer scans through the patient's body and the echoes are displayed on a screen as a function of depth). A further device (*TM3*) was equipped with *B*- or *brightness-mode* ultrasound (also known as *2D mode*). In this mode, an array of transducers is used to obtain a two-dimensional image of a plane through the patient's body. Even if the results with the *TM3* were still not good enough to consider a clinical application, they were crucial to obtain enough funding to keep the research project alive. Further laboratory studies revealed that with two independent, biplane X-ray imaging systems, three-dimensional stone location could be possible. In the *TM4*, ultrasound imaging was replaced by an integrated X-ray system (Chaussy et al. 2007). Initially, the lithotripter had a rubber membrane to couple shock waves into the body of the animal; however, an open water bath was used in the next prototype, because shock wave transmission through the membrane was not as efficient as expected. The first water bath model with a two axis X-ray system for animal studies was finished in 1978. Extensive animal experiments were performed during 1978 and 1979 (Chaussy et al. 1978, 1979b) and finally it was possible to obtain funding to develop the first clinical lithotripter prototype, the Dornier *Human Model 1* (*HM1*) shown in Fig. 2.5. Hoff, Hepp, and Forssmann were in charge of the technical developments.

In 1979 the first *HM1* was installed at the Institute of Surgical Research of the Ludwig-Maximilians University, Klinikum Grosshadern in Munich (Fig. 2.6). Patient positioning inside the water tub was tested on a group of stone bearing volunteers (Chaussy et al. 2007). This lithotripter was used to perform the first SWL treatment on February 7, 1980 by Christian Chaussy, Bernd Forssmann, and Dieter

Fig. 2.5 Photograph of the *Human Model 1* (*HM1*) lithotripter (Dornier MedTech GmbH, Wessling, Germany), used to perform the first extracorporeal shock wave lithotripsy in 1980, showing (*1*) the right (as seen from the patient) and (*2*) the left image intensifier of the biplanar fluoroscopy system, (*3*) the water tub, and (*4*) the patient stretcher. The lithotripter was donated to the German Museum ("Deutsches Museum") in Bonn, Germany. (Courtesy of C. Chaussy)

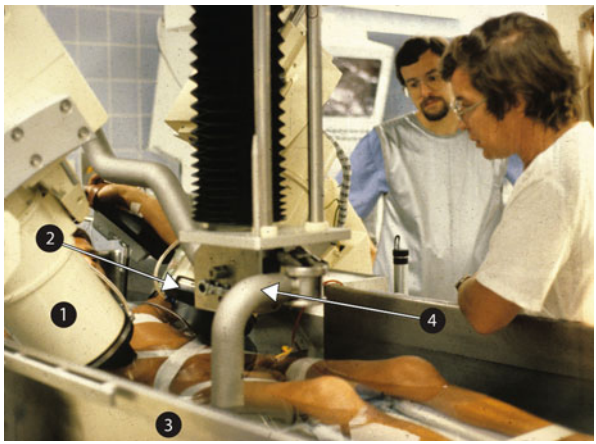


Fig. 2.6 Christian Chaussy (*right*) supervising patient positioning for SWL with the Dornier *HM1* extracorporeal shock wave lithotripter. The photograph shows the two image intensifiers (*1*) and (*2*) of the biplanar fluoroscopy system, the stainless steel water tub (*3*) and the support of the patient stretcher (*4*). (Courtesy of C. Chaussy)

Jocham (Chaussy et al. 1980, 1984, 2014; Brendel 1981). A first trial was actually made at the end of 1979; however, the procedure had to be interrupted before starting the emission of shock waves, because the patient began to float in the water tub, not following the movement of the patient gantry as required. The problem was solved by designing special straps to fasten the patient to the gantry, allowing precise positioning and successful fragmentation of the kidney stone during the memorable SWL in 1980 (Wess 2009). Figure 2.7 is a photograph taken at the tenth anniversary of this first historical treatment.

Fig. 2.7 From *left* to *right*: Christian Chaussy, Egbert Schmiedt and the first SWL patient Hans Dworschak, standing next to a *Lithotripter Compact* (Dornier MedTech GmbH, Wessling, Germany), 10 years after the historical treatment with the Dornier *HM1* at the Klinikum Grosshadern in Munich, Germany. (Courtesy of C. Chaussy)

Fig. 2.8 Photograph of the legendary *Human Model 3* (*HM3*) extracorporeal shock wave lithotripter, showing (*1*) the image intensifiers of the biplanar X-ray system before placing them into the treatment position, and the patient on the stretcher before being positioned inside the water tub (*2*). (Courtesy of Dornier MedTech GmbH, Wessling, Germany)

The novel technique, published at the end of the same year (Chaussy et al. 1980; Chaussy and Staehler 1980) was received with skepticism by the urological community. An abstract dealing with the first results of SWL, which Chaussy and colleagues submitted to the 1981 meeting of the American Urological Association (AUA) was not accepted. Nevertheless, the first clinical experience with SWL was published in the Journal of Urology shortly after (Chaussy et al. 1982). A total of 220 patients were treated with the *HM1*. A second model, the Dornier *HM2* was installed in the first lithotripsy center, headed by Chaussy, at the University of Munich in May 1982. The *HM1* and *HM2* prototypes were followed by the first commercial extracorporeal lithotripter, the *HM3* (Sect. 5.2.1). The first *HM3* (Figs. 2.8 and 2.9) was installed in 1983 at the Department of Urology of the Katharinen Hospital in Stuttgart, under the supervision of Ferdinand Eisenberger (Eisenberger et al. 1983, 1985), and a second device was installed at the Klinikum

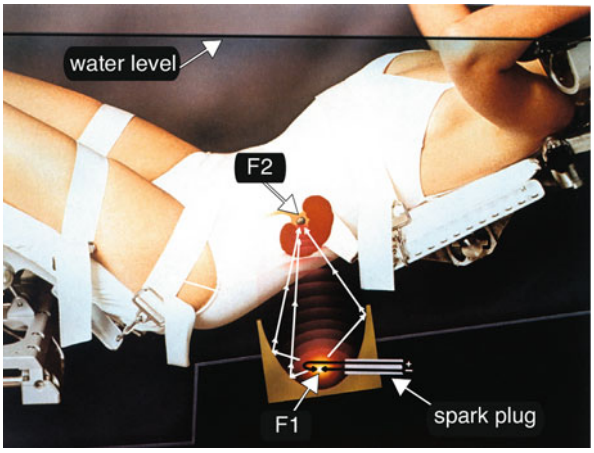


Fig. 2.9 Image of the *Human Model 3* (*HM3*) extracorporeal shock wave lithotripter. Shock waves were generated by underwater electric discharges at the inner focus (*F1*) of a paraellipsoidal metallic reflector and focused towards the outer focus (*F2*). A stationary biplanar X-ray system (not shown) guaranteed localization and positioning of the kidney stone at *F2*. (Courtesy of Dornier MedTech GmbH, Wessling Germany)

Grosshadern in October 1983. Until 1985, the *HM3* was the only extracorporeal lithotripter on the market. It was an expensive high-tech system, consisting of a huge water tub, a biplanar fluoroscopy location system, a shock wave generator, a patient-positioning device, a hydraulic supply system, a water treatment unit, and a control cabinet. As of 1986, more than 20 SWL centers had performed more than 26,000 treatments in West Germany. Worldwide, about 200 Dornier lithotripters were installed and more than 250,000 successful treatments had been performed (Drach et al. 1986), causing a revolution in urinary stone therapy. The Dornier *HM3* was considered to be "the gold standard" of SWL by many authors worldwide (Cass 1995; Lingeman and Safar 1996; Graber et al. 2003; Gronau et al. 2003; Gerber et al. 2005), and in 1998 it was still one of the most widely used lithotripters in the USA. After the initial model, Dornier released the so-called *modified HM3*. This model and the *HM4*, a "dry" lithotripter with a water cushion (Fig. 2.10), had lower energy and a slightly larger reflector aperture to produce a tighter focal zone (Sect. 5.2.1).

The first extracorporeal lithotripter in the USA (an *HM3*) was installed in March 1984 at the Methodist Hospital in Indianapolis and operated by James Lingeman and Daniel Newman. Shortly later, Japan purchased an *HM3* that was installed in a lithotripsy center managed by the doctors Tazaki and Higashihara in Sapporo. The FDA (Food and Drug Administration) of the USA pre-market approval was obtained in December 1984 and the approval of the Japanese Ministry of Public Welfare was attained in November 1985. SWL clinics in Houston, Gainesville, Boston, and Charlottesville followed, and were leaded by Don Griffith, Birdwell Finlayson, Steve Dretler, and Jay Gillenwater, respectively. A report of the United States cooperative

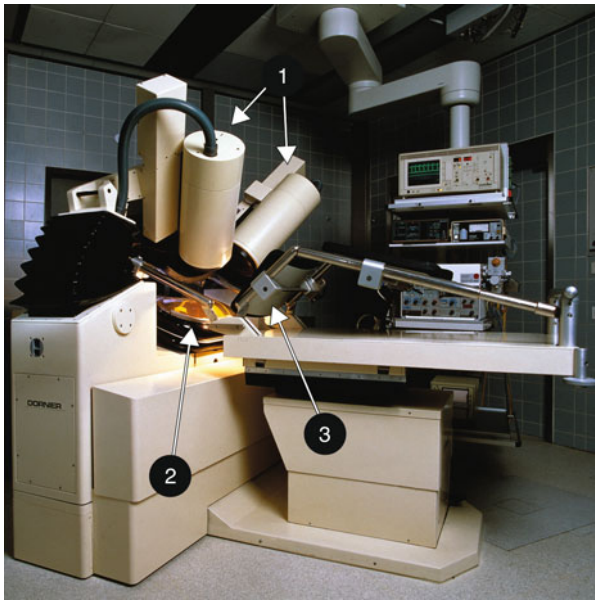


Fig. 2.10 Photograph of the *Human Model 4* (*HM4*) extracorporeal shock wave lithotripter, showing (*1*) the image intensifiers of the biplanar X-ray system, (*2*) the water cushion, and (*3*) the patient stretcher. (Courtesy of Dornier MedTech GmbH, Wessling, Germany)

study of SWL was published in 1986 (Drach et al. 1986). In 1989 Chaussy, Schmiedt, and Eisenberger were rewarded by the AUA with the Distinguished Contribution Award. The Acoustical Society of America held the first session devoted to SWL in 1988.

In 1978, a research project called "Ultra Shock Wave" was started at the company Richard Wolf GmbH (Knittlingen, Germany), in collaboration with the University of Saarland and the University of Karlsruhe in Germany. The main goal of the project, leaded by Herbert Schubert, Helmut Wurster, and Werner Krauss, was to study the feasibility of piezoelectric-based extracorporeal shock wave lithotripsy. After several unsuccessful trials with compact piezoelectric bowls, Günther Kurtze and Rainer Riedlinger from the University of Karlsruhe found a solution by arranging about 3000 small piezoelectric cylinders on a self-focusing spherical bowl made of metal, embedded in a special epoxy resin and activated by a high-voltage pulse (Sect. 5.4.1) (Kurtze and Riedlinger 1988). In December 1985, the first patient with a kidney stone was successfully treated without anesthesia at the University of Saarland Hospital by Manfred Ziegler, Thomas Gebhardt, and Dietmar Neisius with a piezoelectric prototype SWL device. The initial successful treatments lead to the design of the *Piezolith 2200* and *Piezolith 2300* (Richard Wolf GmbH) lithotripters in 1986. These were the first commercially available piezoelectric-based SWL systems (Sect. 5.4.1). The novelty of the *Piezolith 2200* was based on a real-time in-line ultrasound localization system combined with a shock wave source having a large aperture and a narrow shock wave focus for painless treatment without anesthesia and virtually no side effects (Ziegler et al. 1986, 1988; Marberger et al. 1988). The continuous real-time in-line ultrasound imaging concept of the *Piezolith*

2200 was adopted by many other manufacturers. Following models manufactured by Richard Wolf GmbH, such as the *Piezolith 2500*, had an additional X-ray localization system integrated. Almost parallel to the *Piezolith 2200*, a piezoelectric lithotripter called *LT01* (Sect. 5.4.1), with a broader focal zone, was manufactured by EDAP (Vaulx-en-Velin, France) (Vallancien et al. 1988, Miller et al. 1989).

Even if the design of an electromagnetic pressure wave source was published in the beginning of the 1960s by Wolfgang Eisenmenger, flat coil electromagnetic lithotripters (Sect. 5.3.1) were developed until the beginning of the 1980s (Eisenmenger 1962; Wilbert et al. 1987; El-Damanhoury et al. 1991a). The first successful SWL with an electromagnetic lithotripter, developed by Siemens Healthcare GmbH in Erlangen, Germany, was performed in 1986 (Coptcoat et al. 1987). Approximately 3 years after the first SWL with the *HM1*, Eisenmenger patented an electromagnetic shock wave source to produce self-focusing shock waves (Eisenmenger 1983). The system was implemented on a Chinese lithotripter (Sect. 5.3.4) many years later (Eisenmenger et al. 2002).

Because the *HM3* and *HM4* were huge systems, several companies developed smaller, easier to use, and less expensive lithotripters. The *Piezolith 2300* (Richard Wolf GmbH) (Fig. 2.11), the *Lithostar* (Siemens Healthcare GmbH, Erlangen, Germany) (Sect. 5.3.1), the *LT01* and *LT02* (EDAP TMS, Vaulx-en-Velin, France) (Fig. 2.12), and the *Sonolith 2000* (Technomed Medical Systems, Vaulx-en-Velin, France) were the initial competitors of the *HM3*.

At the end of the 1980s, gallstones were successfully treated with a modified kidney lithotripter (Chaussy and Fuchs 1989). This led to the development of a multipurpose device for biliary and urinary stones. Second- and third-generation lithotripters, featuring ultrasonic or fluoroscopic imaging and offering multifunctionality, improvements in patient positioning and decreased anesthesia, were developed; however, according to several authors, it took almost 20 years for the so-called fourth-generation lithotripters to achieve better clinical outcomes than the *HM3* (Rassweiler et al. 2005; Wess 2005; Nomikos et al. 2007).

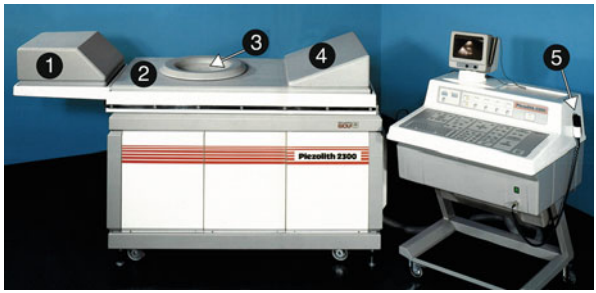


Fig. 2.11 Photograph of the *Piezolith 2300* piezoelectric extracorporeal shock wave lithotripter, showing (*1*) the cushion for the patient's legs, (*2*) the fixed treatment table, (*3*) the open water bath, (*4*) the cushion for the patient's head, and (*5*) the manual ultrasound probe. (Courtesy of Richard Wolf GmbH, Knittlingen, Germany)

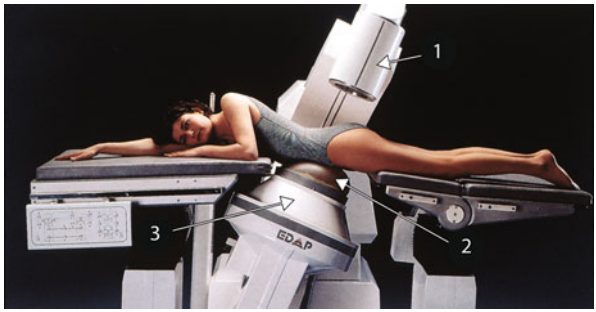


Fig. 2.12 Photograph of the *LT02* piezoelectric extracorporeal shock wave lithotripter, showing (*1*) the mobile C-arm with the fluoroscopy system, (*2*) the water cushion, and (*3*) the shock wave generator with integrated ultrasound probe and X-ray source. (Courtesy of EDAP TMS, Vaulx-en-Velin, France)

As will be described in Chap. 5, most modern lithotripters can be used without anesthesia, are equipped with both fluoroscopy and ultrasound imaging, and allow multifunctional use. Several of these lithotripters can be installed in a relatively small space.

A first step towards compact extracorporeal shock wave lithotripters was made by Direx Systems Corporation (Canton MA, USA), with the introduction of a modular device called *Tripter Compact* (Servadio et al. 1988). Coupling a C-arm and a treatment table to their shock wave generator resulted in a more versatile and affordable system. The idea was soon adopted by other manufacturers (Fig. 2.13). Another ingenious system, developed by Othmar Wess and Ernst Marlinghaus at Storz Medical AG (Tägerwilen, Switzerland), was an electromagnetic shock wave source based on a cylindrical, instead of a flat coil (Wess et al. 1990). As will be described in Sect. 5.3.2, the cylindrical design uses a parabolic reflector instead of an acoustic lens to focus the shock waves. The first patient was successfully treated with this device in 1989. Since then, about 1700 Storz extracorporeal shock wave lithotripters with a cylindrical coil have been installed worldwide.

The first SWL-patient successfully treated for a salivary gland stone (Sect. 5.8) was exposed to shock waves on a piezoelectric kidney lithotripter, since no shock wave equipment for dentistry was commercially available at that time (Iro et al. 1989).

In Japan, microexplosives were proposed to generate shock waves for biomedical applications (Murata et al. 1977; Watanabe and Oinuma 1977; Kaneko et al. 1979; Watanabe et al. 1983). Initial research was performed in 1975 at the Shock Wave Research Center of the Institute of Fluid Science, Tohoku University. Takayama and his research group suspended small lead azide pellets on thin cotton threads in water, igniting them with a laser beam to produce underwater shock waves. In 1982, the results lead to collaborations with the School of Medicine of the same university to explore the potential of microexplosive SWL (Takayama 1993; Takayama and Saito 2004). After successful in vivo experiments (Kuwahara et al. 1986), the first patients

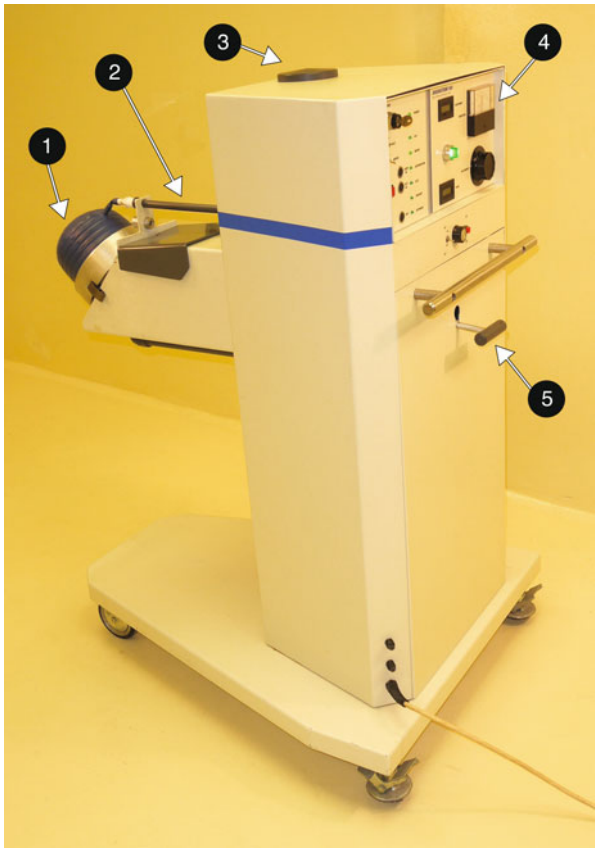


Fig. 2.13 Photograph of the *Breakstone 100* compact electrohydraulic shock wave lithotripter (Breakthrough Medical Corp., Gaithersburg, Maryland, USA), showing (*1*) the water cushion of the shock wave source, (*2*) the air outlet of the water cushion, (*3*) the water reservoir, (*4*) the voltmeter that displays the high-voltage setting, and (*5*) the crank handle to manually move the shock wave source and replace the spark-plug. The device had to be coupled to a patient treatment table and an X-ray C-arm

were treated with a microexplosive extracorporeal lithotripter in 1985 (Sect. 5.2.2). The device was approved for clinical therapy by the Ministry of Health in Japan in 1987 (Kuwahara et al. 1987).

During the early days of SWL, it was not expected that shock waves would be used clinically to treat three other conditions in urology (Chap. 6): the Peyronie's disease (Butz and Teichert 1998), the chronic pelvic pain syndrome (Zimmermann et al. 2005), and erectile dysfunction (Gruenwald et al. 2012). The idea of using shock waves to treat indications other than lithotripsy emerged after incidental observations of a shock wave-induced osteogenic response on living tissue in vivo (Graff et al. 1988a, 1989; Yeaman et al. 1989). One of the first reports indicating that extracorporeal shock wave therapy (ESWT) has the potential to be used prior to revision total hip arthroplasty to facilitate cement and component removal was published by Karpmann et al. (1987). Pioneering studies of ESWT for delayed and nonunion of fractures were reported by Bürger et al. (1991), Valchanou and Michailov (1991), and Schleberger and Senge (1992). The first commercial shock wave source designed specifically for orthopedic and traumatic indications, called *OssaTron* (High Medical Technologies, AG, Lengwil, Switzerland), became available

Fig. 2.14 Photograph of the *OssaTron* shock wave source, designed for orthopedic and traumatic conditions. (Courtesy of High Medical Technologies, AG, Lengwil, Switzerland)

in 1993 (Fig. 2.14). The FDA approved therapy with the *OssaTron* for chronic *plantar fasciitis* and tennis elbow in 2000 and 2003, respectively. During the following years, several clinical applications of ESWT were developed (Thiel 2001). Each application has its own history and the list of conditions is continuously growing. Examples are shock wave therapy to patients suffering from *shoulder tendinopathy* (Rompe et al. 1995b; Haupt 1997), *plantar fasciitis* (Dahmen et al. 1995), tennis elbow (Rompe et al. 1995a), *heel spur* (Cosentino et al. 2001), Achilles tendons (Rompe et al. 2008), ESWT to children with spastic movement disorders (Lohse-Busch et al. 1997), and to patients with cellulite (Siems et al. 2005). ESWT also shows astonishing results in wound healing (Qureshi et al. 2011). The first successful noninvasive shock wave thrombolysis treatment was done in 1998, using a modified *Minilith SL1* (Storz Medical AG) electromagnetic shock wave source (Belcaro et al. 1999). Initial therapies of revascularization with extracorporeal cardiac shock waves were also performed in 1998 (Caspari and Erbel 1999). The *Modulith SLC* (Storz Medical AG), which has a specially modified electromagnetic lithotripter shock wave source, was the first commercial shock wave device to treat ischemic zones of the heart (Sect. 6.17). Today, shock waves are an alternative to treat chronic stable angina pectoris.

Since 1999, not only focused, defocused, and planar shock waves, but also so-called radial shock waves have been used clinically. Radial shock wave sources increased the range of indications of ESWT, although strictly speaking these devices generate radial pressure waves, not shock waves. Nowadays, small desktop

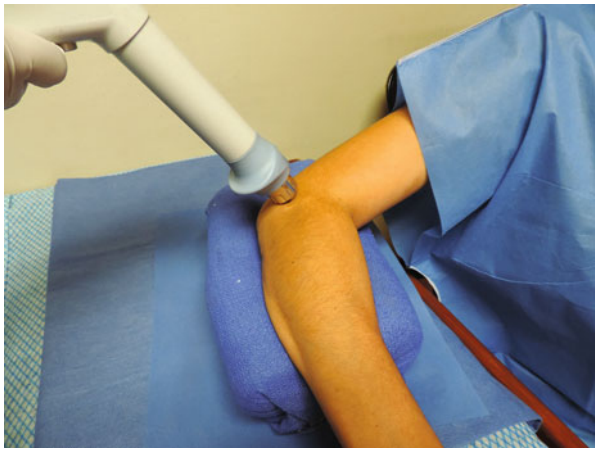


Fig. 2.15 Therapy on the lateral epicondyle with a *5000 SWT Power* radial pressure wave unit (BTL Laboratorios de Tecnología, México). (Courtesy of J. Lozano Pardinas)

devices are common in doctors' offices to treat ailments in a variety of areas, such as orthopedics (Fig. 2.15), dermatology, odontology, neurology, cardiology, and veterinary medicine.

Writing about the history of biomedical applications of shock waves is getting more complicated as time passes, because the developments are spreading into an increasing variety of fields. An example worthwhile commenting is genetic transformation of fungi. Filamentous fungi are valuable microorganisms to produce compounds, such as antibiotics, insulin, hepatitis vaccines, and anticoagulants; however, the process can only be achieved by inserting foreign DNA into their genomes. Unfortunately, standard methods suffer from a low efficiency of genetic transformation and a bad reproducibility. Surprisingly, a few years ago it was discovered that exposure of fungi to shock waves, as used in clinical applications, is a highly efficient transformation method. The first reports on shock wave-mediated genetic transformation of bacteria (Jagadeesh et al. 2004) and fungi (Magaña-Ortíz et al. 2013) already belong to another chapter of the history of biomedical applications of shock waves, which begun long time before in the aerospace industry with the problem of damage caused by raindrops impinging on supersonic aircraft.

Chapter 3
Shock Waves as Used in Biomedical Applications

3.1 Introduction

Shock waves play an important role in several fields, such as acoustics, physical chemistry, aero- and gas-dynamics, materials sciences, space sciences, geosciences, life sciences, and medicine; however, their properties and some definitions may vary from one field to the other. Most literature describing shock waves is specialized and written for readers with a solid background in physics. Furthermore, shock waves are often related to supersonic aircraft. This might be confusing to scientists from non-physical areas, because the relationship to clinically used shock waves is not obvious. If an object such as an airplane or a bullet is traveling at supersonic speed, the waves in front of the object interfere constructively, producing a conical shock front, known as *bow wave*. This occurs because as the object accelerates, the pressure waves ahead of it get closer together, until they cannot escape from the source (object) and pile up in front of it, forming the sonic boom that is heard and felt after a supersonic aircraft has passed. The velocity of sound, divided by the velocity of the object is known as *Mach number*. The Mach number of shock waves in fluids as used in biomedical applications is low (close to one). This is why they are sometimes called *weak shock waves*. Bow waves generated by supersonic aircraft and shock waves as used in biomedical applications have some similarities; however, their generation mechanism is different.

In this chapter basic information on biomedical shock waves is given. The text was written as a guide to students, physicians, biologists, and scientists starting research on clinical and experimental applications of shock waves. Some sections may help to avoid confusions in regard to the definitions commonly used in this field. Equations are kept to a minimum and may be skipped by readers not having the required mathematical background, without sacrificing the understanding of the main concepts.

The physical parameters defined here may be useful to evaluate the output of pressure wave sources; however, at the present time there is still a debate on their correlation to extracorporeal shock wave lithotripsy (SWL) or extracorporeal shock wave therapy (ESWT) efficiency, tissue damage, biological effects, and possible treatment outcome. Before comparing pressure measurements or energy values obtained from these measurements, it is important to describe the methodology that was followed, because results may vary a lot depending on the definitions, the hydrophone, and the coupling media used. The most popular standard to characterize shock wave sources is the IEC 61846 international standard (Ultrasonics/ Pressure Pulse Lithotripters/Characteristics of Fields, International Electrotechnical Commission, Geneva, Switzerland, first edition 1998). It was developed by a worldwide organization for standardization comprising many national electrotechnical committees. Even if the standard was developed for *extracorporeal lithotripters* (also called *lithotriptors*), i.e., the devices used in SWL, it may also be used for ESWT systems, as long as no other international standard is available.

Comparison between clinical shock wave sources should consider several parameters. The physical mechanism of shock wave generation and the purpose for which the devices were designed are also crucial. Some shock wave sources were developed to microscopically cause interstitial and extracellular responses leading to tissue regeneration. These systems produce lower energies than those needed to comminute calculi. Important definitions needed to characterize a shock wave are the *peak-positive pressure*, the *peak-negative pressure*, the *rise time*, the *pulse duration*, the *energy per pulse*, the *energy flux density* (EFD), and *the −6 dB and 5 MPa focal zones*. All of them will be explained in this chapter.

3.2 Pressure and Pressure Waves

Since 1971 the official unit of pressure is the *pascal* (Pa). It is equal to one newton (N) per square meter. Due to historical and practical reasons several other units, such as the *atmosphere* (atm), the *bar*, and the *pound per square inch* (psi), are still popular. In specifications of radial pressure wave sources, also called *ballistic sources* (Sect. 6.3), the bar which is equivalent to 10^5 Pa is used to report the pressure of the air compressor. This pressure value is of no use if information on the model of the ballistic device or if details of the generated pressure waveform and applied EFD (Sect. 3.5) are not given. The *megapascal* (1 MPa = 10^6 Pa = 10 bar) is normally used to report pressure amplitudes in pressure fields generated by biomedical shock wave sources. Because pressure is sometimes measured by its ability to displace a column of mercury in a manometer, it is also expressed in *millimeters of mercury* (1 mmHg ≈ 133.3 Pa). A well-known example is blood pressure.

The *instantaneous pressure* (p) is defined as the pressure minus the ambient pressure at a particular point. *The peak-positive pressure* (p^+) is the maximum compressional pressure value at any point in a pressure field. Analogously, the *peak-negative pressure* (p^-) is the maximum of the modulus (absolute value) of the rarefactional

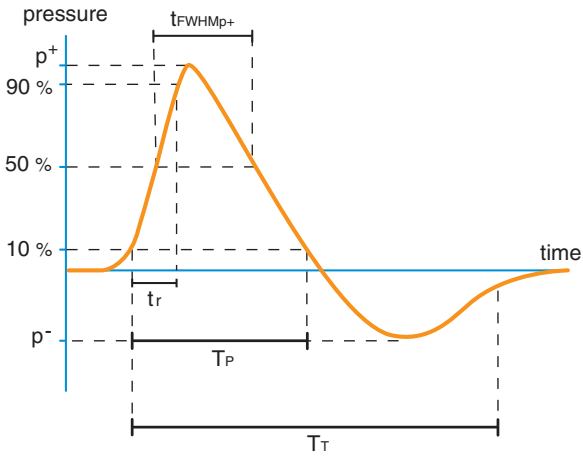


Fig. 3.1 Sketch of a pressure pulse waveform showing the peak-positive pressure (p^+), the peak-negative pressure (p^-), the rise time (t_r), the compressional pulse duration (t_{FWHMp^+}), the positive temporal integration limits (T_P), and the total temporal integration limits (T_T). The rise time was exaggerated for clarity

pressure at any point in the pressure field (Fig. 3.1). It is also common to call p^- *maximum negative pressure* or *peak-rarefactional pressure*. Even if pressure, that is, the force applied perpendicular to a surface per unit area, has as a positive value, depending on the reference defined as zero level, it is sometimes also reported as being negative. An example could be a region where air pressure is lower than atmospheric pressure. In reports dealing with biomedical applications of shock waves, pressure is usually considered to be negative if its value is below the pressure before the shock wave arrives, i.e., the pressure trough appearing after the leading positive pressure pulse is considered to be negative. The absolute value of p^- generated by SWL equipment is smaller than that of p^+; however, the rarefactional pressure pulse generally lasts longer than the positive pulse (Fig. 3.2). If the maximum negative pressure exceeds the cohesion forces of the fluid or adhesion to motes in the fluid, bubbles appear. This phenomenon is called *acoustic cavitation* (Sect. 4.7). In biomedical applications, cavitation commonly forms from small cavitation nuclei or microbubbles.

When reporting a pressure value such as p^+, it is important to mention if it refers to the peak-positive pressure recorded at a specific spot, that is, if it is the peak value of a single pressure record as the one shown in Fig. 3.2, or if it refers to the maximum peak-positive pressure in the whole pressure field of a shock wave source (Fig. 3.3). The same is valid for p^-.

The *positive pulse duration*, *compressional pulse duration,* or *positive pulse width* (t_{FWHMp^+}) is defined as the time from the instant when the pressure exceeds 50 % of p^+ for the first time, to the instant when the pressure drops again to this value (Fig. 3.1). The subscript "FWHM" stands for *full width at half maximum*. It should be followed by a small plus sign or a "p^+", to distinguish it from (t_{FWHMp^-}), which refers to the *negative pulse duration*. The duration of the negative pulse is seldom reported because, as will be explained in the last section of this chapter, obtaining reliable recordings of the tensile phase is complicated.

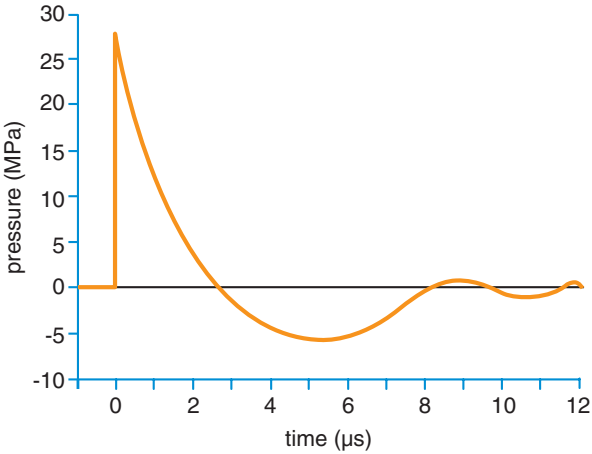


Fig. 3.2 Sketch of the pressure profile of a typical shock wave, recorded at the focal spot of an electrohydraulic extracorporeal shock wave lithotripter

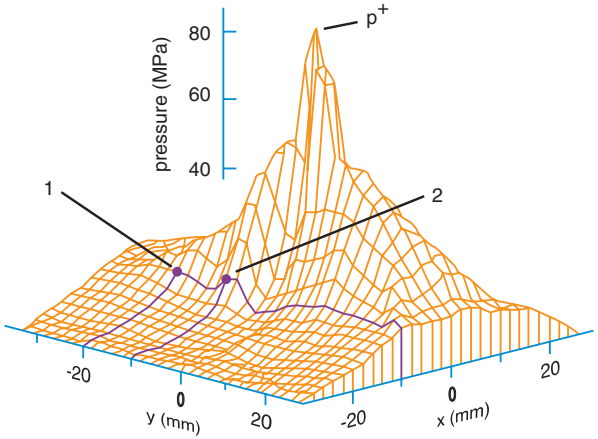


Fig. 3.3 Graph of the average peak-positive pressure values recorded on an *xy* plane perpendicular to the beam axis of a shock wave source. The geometrical focus of the shock wave source is located at (0,0). In this plot $p^+ = 80$ MPa represents the average maximum peak-positive pressure in the whole pressure field, (*1*) corresponds to the average peak-positive pressure measured at the point (−10 mm, −20 mm) and (*2*) represents the average peak-positive pressure at −10 mm, −10 mm). According to standard IEC 61846, the EFD is measured at the location where p^+ is maximum in the sound field, i.e., at the acoustic focus or focal spot. The geometrical focus and the focal spot do not necessarily coincide

The *rise time* (t_r) is a measure of the steepness of the shocked part of the wave and is defined as the time taken for the positive pressure to rise from 10 % to 90 % of p^+ (Fig. 3.1). The values of p^+, p^-, $t_{\mathrm{FWHMp^+}}$ and t_r depend on several factors, such as the shock wave generation principle, the focusing mechanism, and the initial energy. All recordings are limited by the measurement tools and the procedure used.

The nonlinear high pressure impulses with short rise time and a wide frequency spectrum generated by extracorporeal lithotripters (Fig. 3.2) are generally called shock waves, whether they are technically shock waves or not. Actually, it is only the sharp positive pressure jump that should be called *shock front*. The negative peak is not as abrupt as the positive spike and does not have a shock in it. In many publications, pressure waves generated by ballistic sources for extracorporeal pressure wave therapy (Sect. 6.3) are referred to as shock waves, even if their pressure amplitude is lower and their rise time much longer than needed for a shock wave. Strictly speaking, pressure pulses should be called shock waves as long as the forces causing the wave to unshock are instantaneously balanced by the forces distorting the wave to shock, i.e., as long as there is a balance between energy absorption and nonlinear effects. For a shock wave in water the rise time can be expressed as (Cleveland and McAteer 2007):

$$t_r = \frac{5}{\Delta p}\,\mathrm{ns}\cdot\mathrm{MPa}, \tag{3.1}$$

where Δp is the pressure change in MPa and t_r is given in nanoseconds (ns). As the pressure jump increases, the rise time shortens. According to this equation, the rise time for a 50 MPa underwater shock wave is 0.1 ns! The corresponding spatial extent Δx, i.e., the spatial separation between two points with temporal separation Δt can be obtained by:

$$\Delta x = \Delta t c_0, \tag{3.2}$$

where c_0 is the sound speed in water (approximately 1500 m/s). According to this equation, the spatial extent Δx of a 0.1 ns rise time $\left(\Delta t = t_r\right)$ would be 0.15 µm. If, for instance, the positive pulse of a pressure waveform as the one shown in Fig. 3.2 lasts 2.6 µs, its spatial extent would be 3.9 mm. In soft tissue, pressure waveforms get distorted and their spatial extent increases (Ueberle and Rad 2011).

The typical shock wave profile emitted by shock wave sources for SWL consists of a 0.5–3 µs compression pulse and a peak-positive pressure between approximately 10 and 150 MPa, followed by a 2–20 µs rarefaction pulse of up to −30 MPa (Fig. 3.2). Theoretically, t_r can vary from less than a nanosecond to about 500 ns. In ESWT devices t_r lasts much longer. Compared to ultrasound, shock waves have much higher pressure amplitudes (Fig. 3.4). Because of this, nonlinear propagation (Sect. 4.2) has to be considered.

The *beam axis* is an imaginary line from the center of the shock wave aperture to the *geometrical focus F* (Sect. 3.4). In most publications, the beam axis is labeled z axis and the x–y plane is taken as a plane perpendicular to z, which contains F at its center. As will be explained in Sect. 5.2.1, for electrohydraulic shock wave sources equipped with a paraellipsoidal reflector to concentrate the energy, the beam axis is a line that crosses both foci of the ellipse (Fig. 3.5).

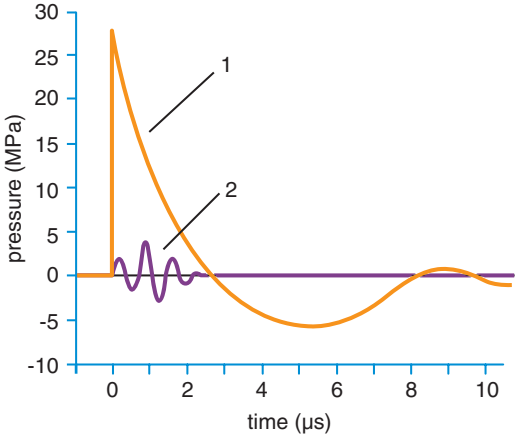


Fig. 3.4 Sketch of (*1*) the pressure profile of a shock wave as used in extracorporeal shock wave lithotripsy, and (*2*) the pressure waveform of a typical diagnostic ultrasound burst

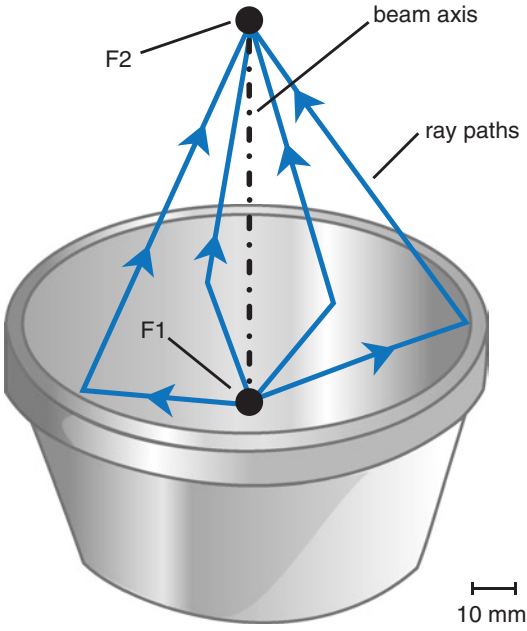


Fig. 3.5 Schematic of an ellipsoidal reflector as used in clinical shock wave sources. Shock waves generated by high-voltage discharges or microexplosives at *F1* are reflected and focused towards *F2*

Contrary to ultrasound which is a single-frequency acoustic wave, the frequency spectrum of a focused shock wave pulse is relatively broad, ranging between approximately 15 kHz and 100 MHz; however; most of the energy lies between approximately 100 kHz and 1 MHz.

For some clinical applications other than SWL (Chap. 6), the terms *radial shock waves*, *radial shock wave therapy* (RSWT), and *radial extracorporeal shock wave therapy* (rESWT) are common, even if they are confusing and physically not correct.

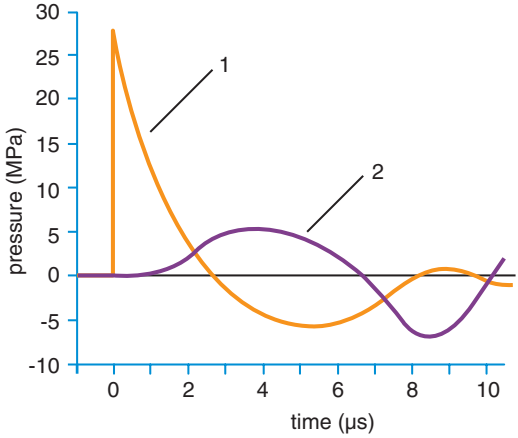


Fig. 3.6 Sketch of (*1*) the pressure profile of a shock wave as used in extracorporeal shock wave lithotripsy, and (*2*) the pressure waveform emitted by radial pressure wave devices (ballistic sources) as used in extracorporeal shock wave therapy

More appropriate are *extracorporeal pressure wave therapy* or *extracorporeal acoustic wave therapy*. To avoid confusions, some companies and authors use the term *extracorporeal pulse activation therapy* (EPAT). Normally, radial pressure waves are generated by accelerating a small projectile inside a closed guiding tube (Sect. 6.3). The bullet strikes a metallic applicator, transforming its kinetic energy into a pressure wave, which expands radially into the target tissue. As already mentioned, a characteristic of radial pressure waves is that their rise time is much longer compared to that of focused shock waves (Fig. 3.6). For some indications, an advantage of radial pressure waves is that they cover a large area so that ultrasound-assisted localization of individual trigger points is not necessary and during a doctor–patient dialogue the so-called biofeedback method can be used successfully (Dreisilker 2010a).

Since shock waves and radial pressure waves are not the same, their modes of action and effects on living tissue are expected to be different. Cleveland et al. (2007) recorded the pressure field produced by a *DolorClast Vet* radial pressure wave device (Electro Medical Systems SA, Nyon, Switzerland) with a polyvinylidene difluoride (PVDF) hydrophone (Sect. 3.6). The pressure pulses were transmitted into a water tank through a membrane. For both the unfocused and the focused applicator, the pressure waveform was similar, consisting of a 4 μs leading positive pulse with a peak pressure of up to 8 MPa, followed by a negative pressure trough and several spikes. The −6 dB focal volume (Sect. 3.4) of this device was not cigar-shaped, as in shock wave sources. It consisted of a volume that extended approximately 40 mm from the applicator when using the unfocused applicator and about 20 mm with the focused applicator. By measuring the rise times of the pressure pulses, the authors concluded that they were too long to be shock waves, i.e., ballistic sources do not produce focused shock waves, even if they are equipped with a focused applicator.

Numerical models that simulate the propagation and focusing of shock waves have been valuable to explain the mechanisms of shock wave action and to design

more efficient shock wave sources. For this purpose, the lithotripter pulse has often been modeled by (Church 1989; Johnsen and Colonius 2008):

$$p = p_0 + 2p_s e^{-\alpha t} \cos\left(\omega t + \frac{\pi}{3}\right), \tag{3.3}$$

where p_0 is the atmospheric or ambient pressure. For the Dornier *HM3* lithotripter (Sect. 5.2.1), the following values have been determined: $\alpha = 1.48 \times 10^8$ s^{-1}, $\omega = 1.21 \times 10^8$ radians/s and $p_s = 35$ MPa.

3.3 Power and Intensity

The *power* of an acoustic wave is defined as the energy carried by the wave per unit of time. Its units are joules per second (J/s), also called *watts* (W). The *instantaneous intensity* (I) of a wave is defined as the acoustic energy transmitted per unit of time and per unit of an area perpendicular to its direction of propagation. In other words, I is the power per unit area or the rate at which the energy transported by the wave passes through a specific area perpendicular to its direction of propagation. It is proportional to the square of the pressure amplitude and its units are watts per square meter (W/m^2). Assuming that the medium is isotropic (equal in all directions) and that the source radiates uniformly, for spherical waves the intensity varies inversely as the square of its distance from the source. If the distance from the source is doubled, the amplitude of the wave decreases by half, and the intensity will only be one quarter of its initial value. To measure sound intensity, logarithmic scales may be useful. It is common to compare the intensity I of a sound wave with a reference intensity I_0 and define the intensity level as:

$$\beta = 10 \log\left(\frac{I}{I_0}\right) \text{dB}. \tag{3.4}$$

For some applications in acoustics the threshold of hearing (10^{-12} W/m^2) is used for I_0. Even if β is dimensionless, it is labeled with units of *decibels* (dB). Actually, the threshold intensity of 10^{-12} W/m^2, corresponding to 0 dB is valid only for a reference frequency of 1 kHz in air. The decibel is normally not used to describe underwater shock wave pressure fields, except for the definition of the *−6 dB focal zone* mentioned in the next section.

For a plane wave, the *instantaneous intensity* (I) can be expressed as the squared instantaneous pressure (p) divided by the *characteristic acoustic impedance* of the medium (Z):

$$I = \frac{p^2}{Z} \tag{3.5}$$

Z may be understood as the resistance to acoustic conductivity and can be calculated as the product of the density (ρ_0) and the sound speed (c_0). For water the acoustic impedance is approximately 1.5×10^6 kg m^{-2} s^{-1}.

3.4 Focal Zones and Penetration Depth

There are several definitions related to the focal zone of a shock wave source. Whether reporting pressure measurements, designing experimental or clinical protocols, or describing the performance of clinical equipment, it is crucial to use the correct terminology. Theoretically, an ideal extracorporeal lithotripter would concentrate all its energy on a volume having the exact shape of the stone or, at least, having the shape of a sphere with a diameter equal to the largest dimension of the stone (Fig. 3.7). This is impossible, since it would require access to the stone from all sides.

In geometrical acoustics, sound waves are treated in a similar way as light rays are considered in optics; however, this simplified theory is valid only under certain circumstances. By definition, the *geometrical focus* is the point where the imaginary rays coming from the shock wave source or from the focusing element (lens or reflector) converge. According to geometrical acoustics, in an electrohydraulic extracorporeal lithotripter, *F2* is the point where all rays generated at *F1* and reflected off the ellipsoidal reflector merge (Fig. 3.8). Because of the popularity of the electrohydraulic Dornier *HM3* lithotripter, the geometrical focus of electromagnetic and piezoelectric shock wave generators have sometimes also been referred to as *F2*. This has no sense, because a second focus only exists when paraellipsoidal reflectors are used to focus the shock waves (Sect. 5.2.1). The location of the geometrical focus can be calculated using the laws of geometrical acoustics; however, in a real scenario, shock waves are not focused at a point (Eliasson 2007).

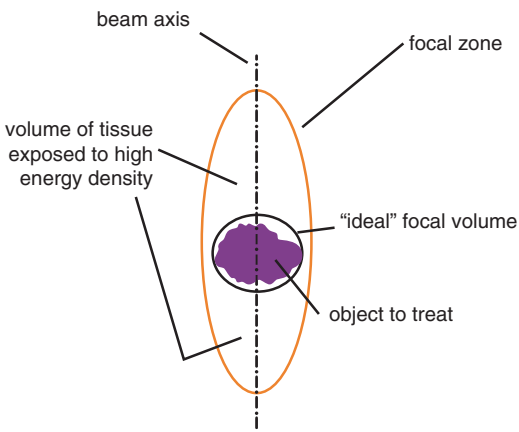


Fig. 3.7 Schematic showing that some tissue surrounding the object to treat will always be at a region of relatively high energy density

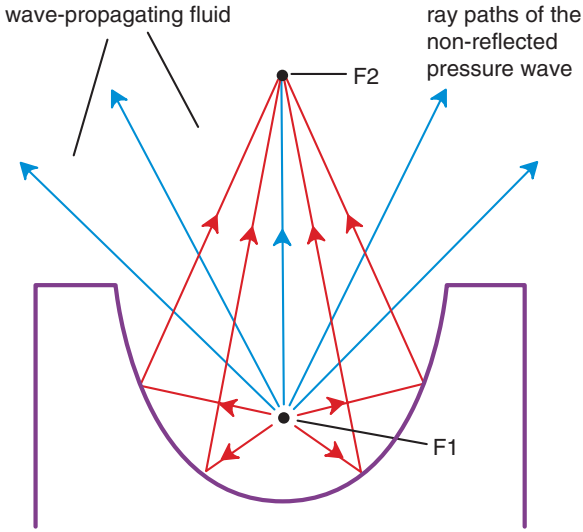


Fig. 3.8 Rays indicating the direction of focused and non-focused shock waves in an electrohydraulic shock wave generator

The point where p^+ is recorded within the whole pressure field of a shock wave source is referred to as *focal spot*, *dynamic focus* or *acoustic focus* (peak of the pressure distribution shown in Fig. 3.3). Because of nonlinear shift, this point normally does not coincide with the geometrical focus. Furthermore, the position of the focal spot varies depending on the energy setting of the shock wave generator. The point where p^- is recorded within the entire pressure field may also be useful to describe a shock wave source. It normally does not coincide with the point of peak-positive pressure. The distance between F^+, i.e., the acoustic focus referred to p^+ and F^-, the focus referred to p^-, is not constant and depends on several factors, such as the shock wave energy and the focusing device. If not specified, the focal spot is related to the peak-positive pressure. It is a common practice to define the *penetration depth* of a shock wave source as the distance from the coupling surface to the *acoustic focus*.

For biomedical applications, the most popular definitions of *focal volume* are (Wess et al. 1997; Ogden et al. 2001b; Cleveland and McAteer 2007): (a) the *−6 dB focal zone*, defined as the volume within which the positive pressure is at least 50 % of its peak value p^+ (Fig. 3.9), (b) the *5 MPa focal zone*, defined as the volume within which the pressure exceeds 5 MPa, and (c) the *10 MPa focal zone*, defined as the volume within which the pressure exceeds 10 MPa. The −6 dB, 5 MPa and 10 MPa focal zones generated by extracorporeal lithotripters have a shape similar to that of a cigar with its longest dimension along the beam axis (Sect. 5.6.4). It is recommended that all manufacturers of extracorporeal lithotripters at least provide the dimensions of the −6 dB and the 5 MPa focal zones of their shock wave sources for the minimum, intermediate, and maximum energy settings.

As mentioned, the −6 dB focal zone, also known as *half-maximum focal zone* or *half-maximum focal volume*, is the volume demarcated by the contour of half the

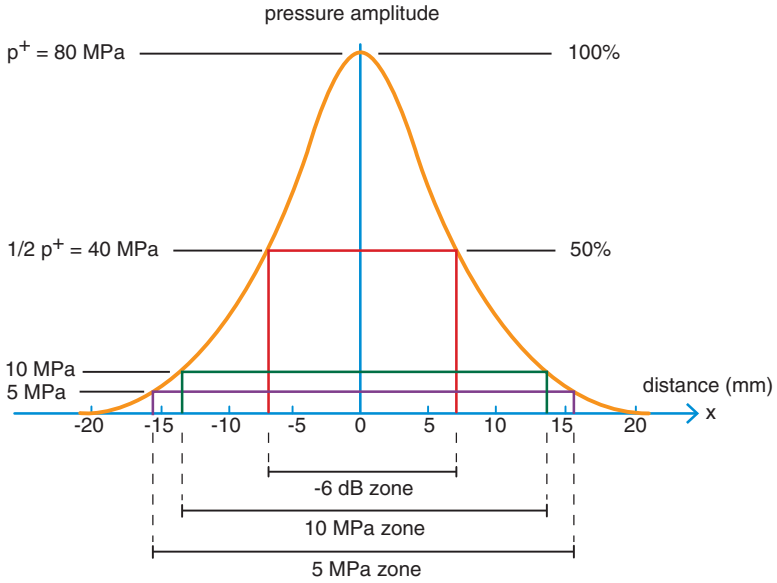


Fig. 3.9 The pressure as a function of the distance along an axis perpendicular to the beam axis of a shock wave source, showing the difference in size between the −6 dB, 10 MPa and 5 MPa focal zones. The peak-positive pressure p^+ of 80 MPa was arbitrarily selected as an example

peak pressure. The region is called −6 dB focal zone, because its isobar corresponds to the pressure being 6 dB less than at the maximum. It is important to have in mind that the −6 dB focal zone gives information on how shock waves are focused; however, it is not a measure of the energy in the focal volume. For SWL considering the −6 dB focal zone as the region at which stone comminution is maximal could be misleading. As shown in Fig. 3.9, sufficiently high pressure values to fragment stones may also be recorded outside of the −6 dB focal zone. In this figure, 80 MPa were chosen as the peak-positive pressure only as an example. The size of the −6 dB focal volume depends on the design of the shock wave source. In general the −6 dB definition refers to the peak-positive pressure; however, it can also be defined in regard to p^-.

Even if the −6 dB zone has been widely used among manufacturers, for clinical applications more information is needed to characterize the pressure field emitted by a shock wave source. A more convenient parameter is the *5 MPa zone*, also called *treatment zone*. It is supposed to be related to the therapeutic effectiveness of shock waves and was defined assuming that the limit of the positive pressure value above which shock waves generate "clinical effects" is 5 MPa. Nevertheless, the 5 MPa value is not supported by scientific evidence and it has to be considered that for biomedical applications other than lithotripsy, lower energies are used successfully (Novak 2014). The German Society of SWL additionally defined the *10 MPa-fragmentation zone*, which is contained inside the 5 MPa-therapy zone (Fig. 3.9).

The energy inside the 10 MPa zone is supposed to be sufficient to comminute urinary stones (Wess et al. 1997; Wess 2004). As the energy of the shock wave generator is raised, both the 5 MPa and the 10 MPa zones increase their size; however, the −6 dB focal zone remains essentially the same.

Analogously to the −6 dB focal volume, the area in the *x*–*y* plane within which the positive pressure is at least 50 % of p^+ is called *−6 dB focal area* or *−6 dB focal cross-sectional area*. Some authors also use an area 12 mm in diameter to calculate the energy delivered to a "standard" stone. The definition of a *12 mm focus* ($F_{12\text{mm}}$) is based on the energy delivered to a spherical stone with a diameter of 12 mm (Wess 2013). Other parameters such as the *disintegration diameter* (Ueberle 2011) have also been proposed. Its size is determined by the volume that is bordered by an increase, by a factor of two, in the number of shock waves needed to pulverize a "typical" stone, as compared to the amount of shock waves needed to disintegrate the same stone in the focus.

3.5 Energy and Impulse

Energy is defined as the capacity for doing work. Energy and work should not be confused with power, which gives information on the *rate* at which work is done and can also be defined as energy flow, i.e., the rate of change of the energy. Most shock wave sources store electric energy in a capacitor bank and abruptly deliver it to a so-called *electro-acoustic transducer* (for instance, electrohydraulic, electromagnetic, or piezoelectric). The electric energy stored in the capacitors is proportional to the energy of the generated shock waves; however, the second value is always significantly smaller. Their relationship depends on the type and the design of the transducer.

An important parameter to characterize a shock wave source is the *energy flux density* (EFD), sometimes also called *energy flux*, *energy density,* or *pulse intensity integral* (PII) (Chitnis 2002; Cleveland and McAteer 2007). It is expressed in mJ/mm^2 and obtained by dividing the acoustic energy by the area, i.e., it is defined as the energy transmitted per unit area per pulse. This measure of energy concentration is useful because the therapeutic effects of shock waves depend, to a certain extent, on whether the energy is distributed over a wide area or focused on a small treatment zone. To obtain the EFD, pressure profiles recorded at various points are needed. Because the pressure fields used in SWL and generated by many ESWT devices have a circular symmetry, the use of polar coordinates is generally convenient. The EFD at a specific point (r,θ) on the *x*–*y* plane is the time integral of the instantaneous intensity:

$$\text{EFD}^+\left(\text{EFD}\right) = \frac{1}{Z}\int p^2\left(r,\theta,t\right)dt, \tag{3.6}$$

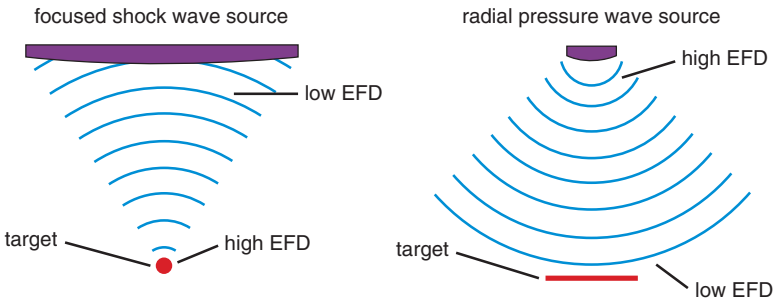


Fig. 3.10 Schematic showing the differences between the pressure field generated by a focused shock wave source and a radial pressure wave source

where p is the instantaneous acoustic pressure. The temporal limits to perform the integration can be either T_P to obtain EFD$^+$, or T_T to obtain EFD (Fig. 3.1). As the distance from the focusing element (reflector or lens) increases, the cross-sectional area of the shock wave beam reduces and the energy density increases. Contrary to this, radial pressure waves as used in ESWT are transmitted radially from the applicator to the target tissue. In this case, the energy density decreases as the penetration depth increases, because the energy is not focused on a treatment target zone (Fig. 3.10).

The *energy per pulse* at the focus is commonly approximated by integration over the −6 dB focal area:

$$E = \frac{1}{Z}\iint p^2\left(r,\theta,t\right)dtdS, \tag{3.7}$$

where S is the focal area in the x–y plane containing F.

It is important to remember that the EFD of two shock wave sources emitting the same total energy E may be different, because the energy density depends on how the pressure wave is focused. The relationship between the electric energy applied to the electro-acoustic transducer and energy values, such as EFD and E depends on nonlinear phenomena and on the focusing mechanism of the shock wave source. Doubling the electric energy will not result in twice as much EFD.

For the same peak pressure, high energy shock waves allow a better fragmentation compared to low energy shock waves (Granz and Köhler 1992). Because shock wave energy is a crucial parameter for stone disintegration and EFD is related to renal tissue damage, as will be explained in Chap. 5, some manufacturers have focused their efforts to enlarge the focal volume in order to achieve high shock wave energy without increasing the EFD. Typical EFD and total pulse energy values for SWL have been reported to be between about 0.2 and 2.0 mJ/mm^2 and between approximately 10 and 100 mJ, respectively (Folberth et al. 1992; Loske 2010); however, some lithotripters, such as the *Modulith SLX-F2 connect* (Storz Medical AG, Tägerwilen, Switzerland) and the *Piezolith 3000* (Richard Wolf GmbH, Knittlingen, Germany) described in Chap. 5, may have even larger EFD and total pulse energy ranges.

For ESWT, the energy flux densities range between approximately 0.004 and 0.6 mJ/mm^2; however, there is no global consensus on threshold values. The classification of the EFD has been inconsistent among different authors. Chow and Cheing (2007) defined low, medium, and high energy flux densities as: lower than 0.1 mJ/mm^2, between 0.1 and 0.2 mJ/mm^2, and higher than 0.2 mJ/mm^2. Bannuru and colleagues (2014) categorized low, medium, and high energy flux densities as less than 0.08 mJ/mm^2, between 0.08 and 0.28 mJ/mm^2 and between 0.28 and 0.60 mJ/mm^2, respectively. Speed (2004) reported low energy flux densities as less than or equal to 0.12 mJ/mm^2 and high energy flux densities above 0.12 mJ/mm^2. For Cacchio et al. (2006) low energy flux densities are lower than 0.10 mJ/mm^2 and high densities are between 0.20 and 0.40 mJ/mm^2.

Many articles on tumor growth suppression report the use of "high-energy" shock waves (HESW) (Russo et al. 1986; Oosterhof et al. 1990a, b; Gamarra et al. 1993a, b; Oosterhof et al. 1996; Frairia et al. 2003; Canaparo et al. 2006). However, the term HESW might be confusing, because energies not higher than standard lithotripter energies were used in these studies.

As already mentioned, in ESWT it is important to distinguish between shock waves and radial pressure waves, which have a lower peak pressure and a much longer rise time than extracorporeal shock waves (Fig. 3.11). Furthermore, the general distinction between radial pressure waves as "low-energy" and shock waves as "high-energy" phenomena is inconvenient (Schmitz et al. 2015).

A good indicator for assessing urinary stone disintegration capacity is the *effective energy*, referred to as E_{12mm} or E_{eff} (Granz and Köhler 1992). It is defined as the energy (in mJ) transmitted by each single shock wave through an area of 12 mm in diameter within the focal plane. As already mentioned, the 12-mm diameter is considered as the diameter of the cross section of a typical stone treated with SWL.

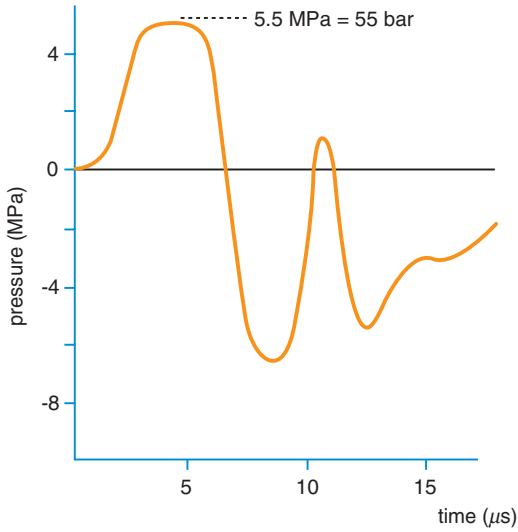


Fig. 3.11 Sketch of the pressure profile generated by a ballistic ESWT source

The effective energy is obtained by integrating the EFD over a 12-mm area, that is, the time integral of the pressure pulse, followed by an area integral. Because the pressure field emitted by lithotripters is symmetric around the beam axis, it is sufficient to measure the pressure along one axis in the focal plane to calculate the energy. The *energy dose* (E_{dose}) is defined as the effective energy E_{12mm}, multiplied by n, the number of applied shock waves.

As previously mentioned, waveforms recorded at various points of the pressure field are needed to calculate the EFD. In the case of ballistic sources (Sect. 6.3), hydrophones capable of recording not only high but also low frequencies (<5 kHz) are required to faithfully register radial pressure waves traveling through tissue phantoms. Low intensity high frequency oscillations are generated by the impact of the projectile inside the transmitter and superimpose with the lower frequency pressure wave. Nevertheless, the influence of the high frequency oscillations is low, because their penetration depth is short (Novak 2014).

The *impact* or *impulse* (J) at the skin surface, i.e., the integral of the force with respect to time, given in Newton seconds (Ns), has been proposed as a parameter to compare different ballistic sources (Novak 2014):

$$J = \int F(t)\,dt \tag{3.8}$$

where $F(t)$ is the force as a function of the time t. As occurs with the EFD, the exact relationship between J and the biological effects on tissue is unknown. J may be used to compare radial pressure wave sources, but should not be interpreted as a measure of biological "effectiveness."

3.6 Recording of Acoustic Cavitation and Shock Wave Fields

Comparison and evaluation of shock wave sources became especially important during the 1980s with the rising of different lithotripter manufacturers and models. The performance of extracorporeal shock wave lithotripters (Sect. 5.6.12) has been evaluated using several methods, such as recording the pressure field in the vicinity of the focal spot (Hunter et al. 1986; Coleman and Saunders 1989; Müller 1990), performing in vitro stone phantom fragmentation (McAteer et al. 2003; van Cauwelaert 2004), capturing the acoustic emissions produced by collapsing bubbles (Sect. 4.7), exposing thin metallic foils to shock waves, using laser scattering and fiber-optic transmittance measurements to provide the time history of bubble dynamics (Huber et al. 1994; Delacrétaz et al. 1995; Jöchle et al. 1996), and high-speed photography recordings (Huber et al. 1999a). This section only describes the basic physical principles of a few systems to record pressure waveforms and cavitation events.

Because of the high frequencies involved and the extremely fast pressure changes, recording of shock waves as used in biomedical applications is challenging. Sensors

that respond linearly over a wide frequency range, having rise times on the order of nanoseconds are needed. Sound reflections at the solid surface of the hydrophone can produce interference and small alignment errors may affect the results. Furthermore, faithfully recording the complete waveform of a shock wave as used in clinical applications is problematic, because the adhesion between the hydrophone and the fluid (water) must be strong enough to withstand the tensile pulse of the shock wave. Moreover, the sensors must resist pitting due to the impact of shock wave-induced microjets (Sect. 4.7).

To evaluate shock wave sources it is recommended to use a sampling interval smaller than 1 mm or one fifth of the minimum width of the −6 dB isobar in the x–y plane. If the value of p^+ from one sampling point to another does not differ by more than 10 %, the sampling intervals may be extended. The IEC 61846 standard defines the parameters which should characterize the acoustic fields and the pressure waveforms generated by clinical shock wave sources. As mentioned before, even if this standard was conceived for extracorporeal shock wave lithotripters it can also be used, to some extent, to evaluate ESWT devices. The standard establishes that hydrophones for biomedical shock wave measurements should have an overall frequency response flat to within ±3 dB between 0.5 and 15 MHz. A further requirement is that the active element should have a diameter equal to or less than 1 mm. There are relatively few commercially available hydrophones designed to evaluate pressure fields produced by shock wave sources for SWL and ESWT.

Recording pressure waveforms at the focal zone is crucial to obtain information on the EFD, as well as other important parameters, such as $t_{\mathrm{FWHM}p^+}$, t_r, p^+, and p^- (Sect. 3.2). Some manufacturers report in-house pressure measurements without describing their methodology. Such measurements are of little value to compare the performance of clinical devices, unless all measurements were done with the same hydrophone and following the same protocol.

Capacitance hydrophones were used by some authors in the early days of SWL (Filipczynsky and Etienne 1990). They proved to be resistant and permitted direct calibration based on electrical measurements; however, the trailing negative phase of the shock wave was not reproduced faithfully. A few years later, Etienne et al. (1997) reported results of pressure measurements with a simple and inexpensive electromagnetic hydrophone. The device relied on the electromotive force induced in an electrical conductor which vibrated under the action of each shock wave inside a magnetic field (Filipczynsky 1969) and was calibrated by measuring the magnetic field of a permanent magnet and the voltage induced in the conductor. The bandwidth of this hydrophone was limited to 17 MHz.

Commercial *piezoelectric pressure sensors* such as the *603B1* (Kistler Instruments Corporation, Switzerland) were also helpful; however, their rise time of one microsecond was too long and the sensitive element of about 5.5 mm too large to faithfully record the pressure fields of extracorporeal lithotripters. Nevertheless, since these hydrophones are easy to handle, have a long service life, provide reproducible measurements and are very resistant, they have been used to perform preliminary measurements.

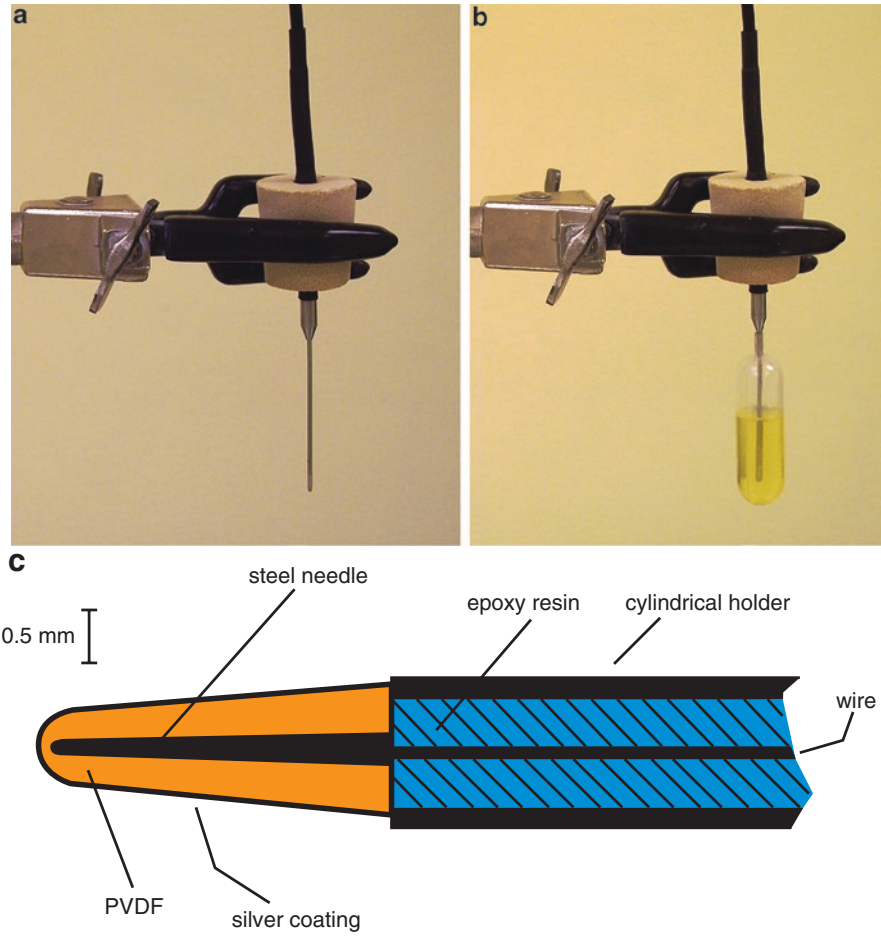


Fig. 3.12 Photograph of a needle polyvinylidene difluoride (PVDF) hydrophone, manufactured by Imotec GmbH in Würselen, Germany (**a**) without a vial and (**b**) inside a fluid filled polypropylene vial (Photographs: F. Fernández). (**c**) Schematic showing the design of a needle PVDF hydrophone. Adapted from Platte (1985)

A popular sensor, especially designed to record lithotripter shock waves is the *needle polyvinylidene difluoride* (PVDF) *hydrophone* (Imotec GmbH, D-5102 Würselen, Germany) developed in 1985 (Müller and Platte 1985; Platte 1985; Müller 1987; Sommerfeld and Müller 1988; Müller 1990). Its working principle is based on the piezoelectric properties of polarized PVDF. The molecules of this polymer can be oriented so that when stressed between a pair of electrodes, a net electrical charge is produced on the electrodes. The hydrophone consists of a steel needle covered with PVDF and silver coating at the tip, glued with epoxy resin into a metallic cylindrical holder (Fig. 3.12). The diameter of the tip is approximately 0.5 mm and the sensor has a rise time of about 20 ns. A disadvantage is that the

water–metal shielding adhesion at the tip of the gauge does not withstand the tensile phase of a shock wave. As a consequence, the duration and amplitude of the negative pulse is underestimated. This has to be considered when calculating energy values from pressure records obtained with needle hydrophones. Furthermore, high-speed fluid microjets produced by acoustic cavitation (Sect. 4.7) may damage the tip of the sensor. It should also be considered that ringing caused by the positive pressure peak may not have disappeared completely before arrival of the tensile pulse. In spite of this, needle hydrophones are easy to use and provide reproducible results. They have been common for many years to study in vitro and in vivo pressure fields generated by extracorporeal lithotripters. Today, other models of PVDF hydrophones having a variety of sensitive diameters, sensitivities, and bandwidths are on the market (Fig. 3.13).

Well suited for recording lithotripter shock waves are PVDF *membrane hydrophones* (Preston et al. 1983; Schafer 1993; Maxwell et al. 2006). These wide bandwidth sensors use the same physical principle as needle hydrophones to convert pressure variations into electrical signals. An advantage compared to needle hydrophones is that they do not produce artifacts due to wave reflections at the tip of the probe; however, since PVDF is hydrophobic, the adhesion between the foil and the water is relatively weak. Because of this, the tensile phase of the shock wave produces cavitation at the contact surface, generating erosion and limiting its ability to reproduce the negative pulse faithfully. Most research groups use membrane hydrophones only for calibration purposes, because they reproduce lithotripter waveforms better than needle hydrophones but are more expensive and cannot be refurbished as easily as needle hydrophones or as the fiber-optic hydrophones described below.

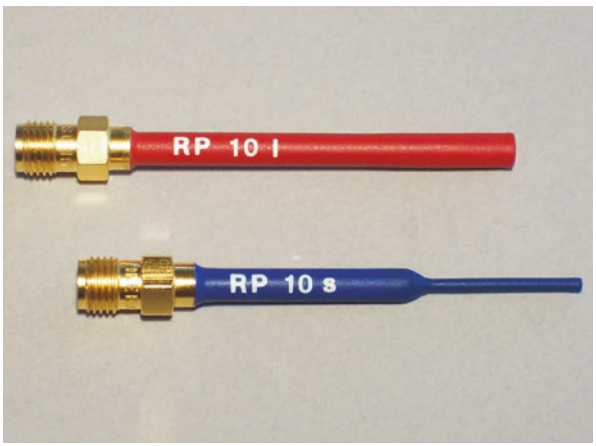


Fig. 3.13 Photograph of two polyvinylidene difluoride (PVDF) needle hydrophones. The red hydrophone (model RP 10 l) has a sensitive diameter of 3 mm, and a sensitivity of 15 mV/bar. The blue hydrophone (model RP 10 s) has a sensitive diameter of 1 mm, and a sensitivity of 2 mV/bar. Both models have a bandwidth ranging from 1 kHz to 3 MHz (Courtesy of RP Acoustics e.K., Leutenbach, Germany)

Granz (1989) developed a reliable PVDF hydrophone by separating the non-metalized sensitive area and the metallic electrodes, i.e., no metal contacts were on the PVDF close to the sensitive region. The shock wave generated alternating charges in a region where the PVDF foil was polarized and piezoelectric. The signal was coupled by a dielectric medium, such as deionized water, to the metallic electrodes located outside the sensitive area. The device was tested over a large bandwidth without any significant decrease in sensitivity. The sensitivity of the PVDF foil was high enough to allow measurement areas as small as 1 mm in diameter.

In 2006 a research group of the University of Washington in Seattle reported results with a novel PVDF membrane hydrophone (Maxwell et al. 2006). The device withstood measurement of up to 1000 lithotripter shock waves and had a low signal to noise ratio. Kreider et al. (2009) reported simultaneous acoustic field measurements of individual lithotripter shock waves using a self-made linear array hydrophone consisting of 20 PVDF elements, each 4 mm long by 0.5 mm wide. Using this hydrophone there was no need to average the measurements done at single locations over several shock waves in order to assess the characteristics of the focal zone. According to the authors, a protective coating or immersion in oil improved the consistency of their device.

Nowadays most pressure measurements are done with *fiber-optic hydrophones* (Eisenmenger and Staudenraus 1991; Staudenraus and Eisenmenger 1993; Wang et al. 1999a, b; Ginter et al. 2002; Parsons et al. 2006b; Ueberle and Rad 2011; Kang et al. 2014). In this system, the tip of a light guiding glass fiber is immersed into water and used as a pressure sensitive element. The fiber-optic hydrophone (FOPH), invented by W. Eisenmenger and J. Staudenraus, has a wide bandwidth and is free from electromagnetic noise. Its operation is based on variations of the refractive index of a fluid, usually water, occurring when the density of the fluid changes (Staudenraus and Eisenmenger 1993). As shown in Fig. 3.14, laser light is coupled into a glass fiber and reflected off its tip. Pressure-dependent density changes at the tip of the fiber result in modulation of the reflected light intensity, which is captured by a photodetector and converted via a directional fiber coupler into a voltage vs time signal (Krücker et al. 2000; Parsons et al. 2006b). Deconvolution or filtering of the measured signal is

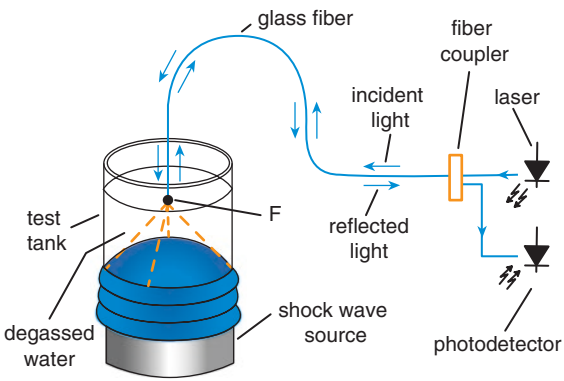


Fig. 3.14 Schematic of the working principle of a fiber-optic probe hydrophone (FOPH)

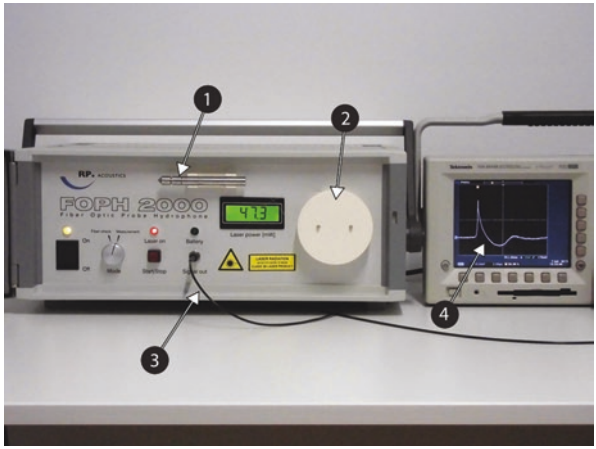


Fig. 3.15 Photograph of a fiber-optic probe hydrophone, showing (*1*) the fiber-optic holder, (*2*) the fiber-optic cartridge, (*3*) the signal output, and (*4*) the recorded pressure waveform after filtering. The fiber is too thin to be seen on this image. (Courtesy of RP Acoustics e.K., Leutenbach, Germany)

recommended. The *FOPH 2000* shown in Fig. 3.15 (RP Acoustics e.K., Leutenbach, Germany) has a high temporal and spatial resolution and is suitable for the measurement of the negative pressure pulse, because the water-glass adhesion is strong enough (Staudenraus and Eisenmenger 1993; Hamilton and Blackstock 1997). According to the manufacturer, the measuring range goes from −60 to 400 MPa, the pressure resolution is ±0.7 MPa and its sensitivity 2 mV/MPa. Another advantage is that the diameter of the active area (spatial resolution) is only 100 μm. Furthermore, the *FOPH 2000* is self-calibrating, i.e., there is no need for a calibration by comparison with a reference standard, because the device can be used as a measuring standard itself (Staudenraus and Eisenmenger 1993). Main disadvantages are its high cost and the fact that the glass fiber may be too fragile to withstand the pressure variations and cavitation events. If the tip of the fiber breaks, it has to be cut and stripped using a fiber cutting tool delivered by the manufacturer. After doing this, the device has to be calibrated and repositioned again. This process is easy but relatively time-consuming. Repairing the fiber can be done at least 400 times, because the cartridge has a fiber length of 20 m. With a fiber-optic hydrophone recording pressure waveforms generated by planar pressure wave sources or radial pressure wave sources is easier than measuring focused lithotripter shock waves, because the fiber tip is not damaged as often as occurs when measuring shock waves. Due to the high accuracy of the FOPH, proper alignment of the fiber is crucial. Fiber-optic hydrophones are not recommended to measure pressure peaks less than 2 MPa. In cavitating liquids large variations in the signal amplitude may be recorded; however, this occurs with any type of pressure probe. Degassing the water in the test tank improves the performance and reduces the probability of damage to the fiber by bubble collapse. Zijlstra and Ohl (2008) reported that by adding a small amount of acetic acid, cavitation and shot-to-shot variations are reduced.

An alternative to the fragile glass fiber of the FOPH is the *light spot hydrophone* (LSHD) proposed by Granz et al. (2004). It is based on the same physical principle as the FOPH; however, the active surface of the LSHD is a glass block (thickness

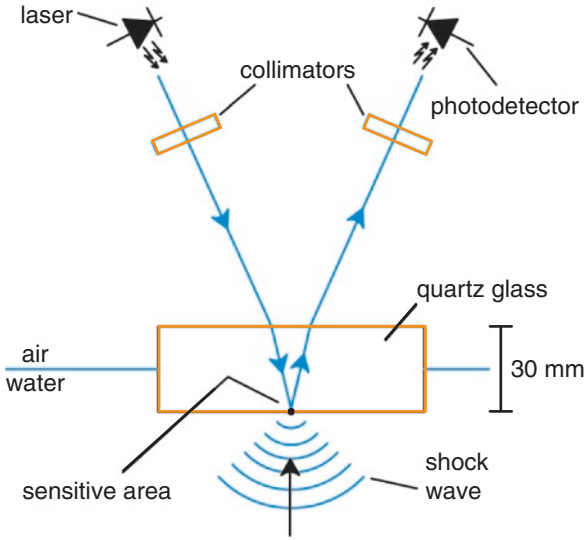


Fig. 3.16 Schematic of the working principle of a light spot hydrophone (LSHD)

about 30 mm) that withstands the action of shock waves and cavitation much better than a glass fiber. As in the FOPH, the intensity of the reflected beam is modulated by changes of the refractive index of the water caused by pressure variations. The front surface of the glass block has to be aligned perpendicular to the focal axis of the shock wave source.

Physicists from the University of Erlangen and engineers from Siemens Healthcare GmbH (Erlangen, Germany) developed an LSHD consisting of a laser focused on and reflected off one side of a quartz glass block, partially immersed in water (Fig. 3.16). The good adhesion of quartz glass to water prevents cavitation at the glass–water interface. The diode laser light passes through a fiber and is directed through the glass block at an angle of about 15° by a lens to a 50 µm spot at the exit-side of the block, which is the sensitive area (Ueberle and Rad 2011). The reflected light is focused by a second lens and coupled into a photodiode. The hydrophone complies with the requirements of the standard IEC 61846 and proved to be as precise as the FOPH. In case that the glass surface gets partially damaged, it is possible to continue with the measurements by just moving the light spot along the glass–water interface to an undamaged area. This reduces the measurement time compared to the use of an FOPH. Comparing measurements carried out on shock wave sources as used for SWL with the FOPH and the LSHD revealed that for high energy settings the LSHD shows a higher peak-negative pressure, probably because of the strong adhesion of quartz glass to water. Good agreements were obtained for the positive peak pressures at both low and high energy settings (Smith et al. 2012). Using a post-processing technique proposed by Rad et al. (2014), the LSHD is reliable for high-pressure measurements. An inconvenience when using the LSHD is that it always needs to be positioned at the water surface, while the shock wave source must be on the bottom of the water tank, i.e., the shock wave beam must impinge vertically on the hydrophone. Another disadvantage is that ascending bubbles may be trapped by

the glass block and produce interferences. Furthermore, the water level must be adjusted if pressure measurements along a vertical axis (z-axis) are required.

The aforementioned hydrophones can also be used to record the pressure waveforms emitted by ballistic pressure pulse sources; however, well-standardized methodologies are still needed. Ueberle and Rad (2012) developed a water-free arrangement to record pressure waveforms generated by ballistic sources. The method can be used for quality control in service and production. The applicator is coupled via a 5 mm silicon layer to a pressure transducer. Using this system on commercial ballistic sources, the authors demonstrated high output variations when the first 10–20 pulses were produced at rates higher than 2 Hz. Comparisons between underwater and dry pressure measurements showed that the novel test bench is a reliable solution to characterize ballistic pressure pulse sources. Pressure waveforms can be recorded with the same accuracy as in water while changing the pulse rate and air pressure of the device. An advantage of the water-free method is that cavitation is avoided.

Not only pressure measurements but also visualization of the pressure field is useful to evaluate pressure wave sources. Shock wave propagation and bubble dynamics can be visualized using optical techniques, such as schlieren photography (Kolacek et al. 1988; Carnell and Emmony 1995a, b; Settles 2001; Yamamoto et al. 2014), high-speed photoelastic techniques combined with shadowgraph imaging (Xi and Zhong 2000; Xi and Zhong 2001; Zhou and Zhong 2003; Oshita et al. 2012), holographic interferometry (Takayama 1983; Hosseini and Takayama 2004), and background-oriented schlieren techniques (Yamamoto et al. 2015). As an example, Fig. 3.17 shows a sequence of schlieren photographs combined with photoelastic stress imaging of a small acrylic cylinder exposed to an underwater shock wave. The diameter of the cylinder (20 mm) was chosen to be comparable to a kidney stone. The underwater shock wave with a peak-positive pressure of approximately 70 MPa, generated using an electromagnetic shock wave source (Storz Medical AG) hits the cylinder from the top of the images. Stress inside the target appears as soon as the shock wave approaches the cylinder (Fig. 3.17b). Small bubbles generated after shock wave passage are visible as dark dots in all images. Spherical secondary shock waves, produced after bubble collapse, can be seen as thin white circles in Fig. 3.17g, h. Another instructive color-schlieren image is presented in Fig. 3.18. Positive and negative pressure variations are displayed in different colors, facilitating the understanding of the phenomenon. Cavitation bubbles generate secondary shock waves after passage of the original shock wave, which propagated from the bottom to the top of the image.

A popular method to study bubble dynamics near the focus of a shock wave source is *passive cavitation detection* (PCD) (Coleman et al. 1996; Bailey 1997b; Cunningham et al. 2001; Bailey et al. 2005; Chitnis and Cleveland 2006; Tu et al. 2007; Collin and Coussios 2011; Wan et al. 2015). An ultrasonic sensor records the acoustic emissions from cavitation without interfering with the cavitation field itself. The received signals are processed to obtain the frequency components of different types of cavitation. Both focused and unfocused PCD have been useful. In the first case, the system provides high spatial specificity and sensitivity in the focal zone of the shock wave source. Unfocused detectors have a lower spatial specificity and sensitivity, but send information from a larger volume of the cavitation field.

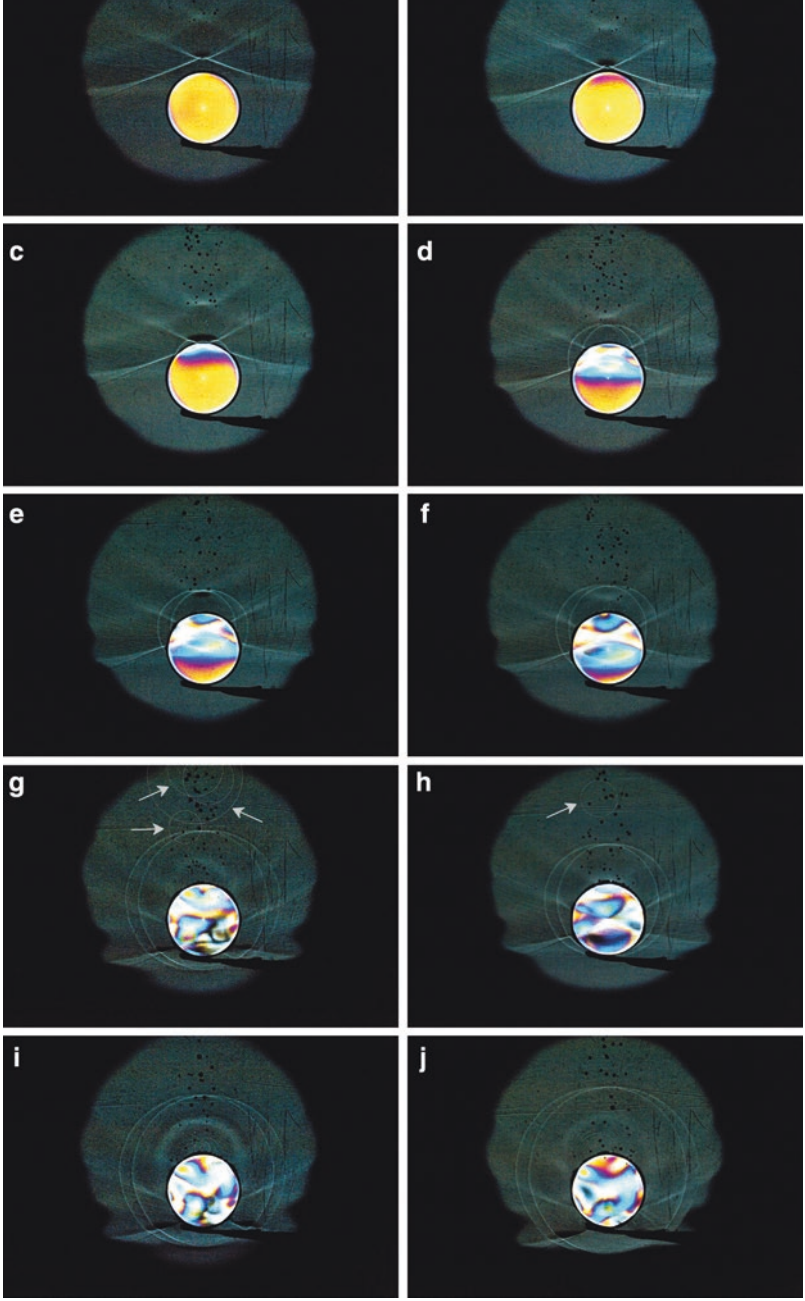


Fig. 3.17 Photographic sequence of an underwater shock wave hitting an acrylic cylinder (20 mm in diameter) from the top of the images, showing the reflected waves in different phases. The colors (*eBook*) display a stress pattern inside the cylinder. Secondary shock waves generated by shock wave-induced bubble collapse can be observed in images (g) and (h) (see *arrows*). Cavitation bubbles are distinguished as *black dots*. Technique: schlieren optics in combination with photoelastic stress imaging (Photographs: O. Wess and J. Mayer, Storz Medical AG, Tägerwilen, Switzerland)

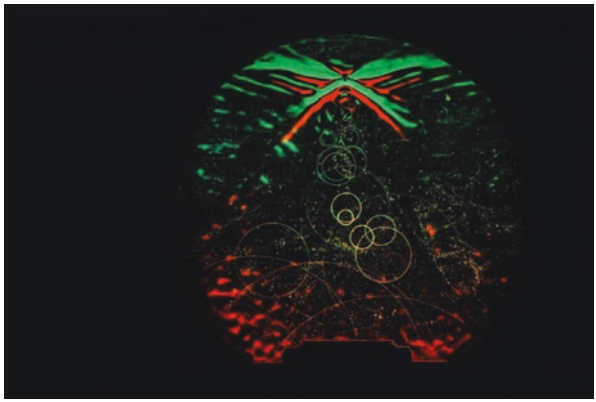


Fig. 3.18 Shock wave focusing close to the focal point of an electromagnetic shock wave source, generating cavitation in water. Collapsing bubbles (*lower part*) create secondary spherical shock waves (*circles*). Technique: color-schlieren optics displaying positive pressure gradients in *red* and negative pressure gradients in *green* (*eBook*) (Photograph: O. Wess and J. Mayer, Storz Medical AG, Tägerwilen, Switzerland)

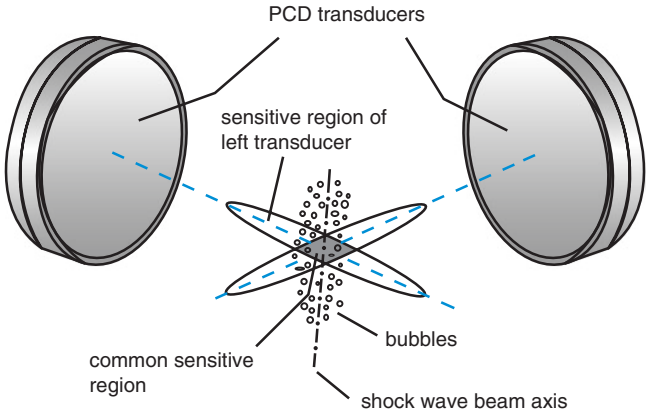


Fig. 3.19 Schematic of a dual passive cavitation detector to record acoustic emissions from cavitation generated at the focal region of an underwater shock wave source. Adapted from Cleveland et al. (2000b)

Other authors (Cleveland et al. 2000b) have used so-called *dual passive cavitation detection* (DPCD), i.e., two nearly orthogonal focused sensors to localize cavitation events. The advantage of this arrangement is that the resulting sensitive volume is small (a few cubic millimeters) and only signals originated from bubbles inside this volume are captured simultaneously by both detectors (Fig. 3.19). Another possibility is to use one sensor to send a wave toward the bubble cloud, while the other transducer receives the reflections from the bubbles. This method, referred to as *active cavitation detection* (ACD), has been tested to study bubble dynamics in biomedicine (Wan et al. 2015). An interesting feature of cavitation detection is in vivo bubble activity recording.

Chapter 4
Shock Wave Interaction with Matter

4.1 Introduction

The interaction of shock waves with matter is a vast and multidisciplinary field and although considerable progress has been made to understand the phenomena involved, there are still questions to be answered. Several subjects discussed here have been the title of books dealing only with that specific topic. This chapter is written for graduates, academicians, and scientists from a broad variety of disciplines. Technical language is used as less as possible and even if some words or equations may not be obvious for all readers, this will not prevent from understanding the main concepts described. The text should provide the reader with an overview of the subjects; however, it is not structured as a textbook that describes concepts step by step. Non-conventional designs and research results have been included to enrich the panorama. The most relevant topics for the purpose of this book are urinary stone comminution mechanisms, and the exposure of bony structures and soft tissue to pressure pulses. For some biomedical applications, the secondary effects of shock wave passage are more important than the direct influence of the shock wave itself. Shock wave-mediated cell transfection, the genetic transformation of microorganisms with shock waves, and the bactericidal effect of shock waves will be discussed in Chap. 7, even if these topics also involve the interaction of shock waves with matter (cells).

During the first years of extracorporeal shock wave lithotripsy (SWL) little information on shock wave interaction with urinary stones and living tissue was available. It is surprising that even many years after the clinical introduction of the *HM3* lithotripter (Dornier MedTech GmbH, Wessling, Germany) there was no complete understanding of these effects. Nowadays, there is a consensus that calculi are pulverized mainly due to spallation, erosion by acoustic cavitation, circumferential compression, tensile and shear stress, fatigue, and superfocusing. Even if these mechanisms act synergistically, rather than independently (Zhou et al. 2004a, b), some of them are more important at the beginning of the treatment and others are crucial at the remaining part of the therapy.

To study the interaction of shock waves and radial pressure waves with living tissue during extracorporeal shock wave therapy (ESWT) is a challenge. The fact that different pressure waveforms produce different biological reactions complicates the scenario even more. Basic research is still needed to better comprehend the phenomena involved. Shock wave-induced tissue damage is the result of complex physical and biochemical mechanisms acting simultaneously and it is important to know that any shock wave or pressure pulse source may cause severe injury if not used properly. A detailed analysis of pressure wave interaction with matter is beyond the scope of this book and only a small percentage of published research will be discussed. Some specific shock wave and radial pressure wave effects on tissue are also described in Chap. 6.

4.2 Propagation and Attenuation

Mechanical waves, such as sound waves, seismic waves, ultrasound, and shock waves, originate from a source, causing a *disturbance* and are a way for energy to be moved from one place to another. In general, a mechanical wave is an alternating compression and relaxation propagating through the medium, affecting the pressure, the density, and the velocity of the molecules. Since energy is imparted to the medium, part of it is displaced, producing vibration of its molecules. This vibration spreads throughout the medium. The initial energy is transferred from one molecule to another. All mechanical vibrations depend on a restoring force provided by intermolecular forces. In order to transmit a periodic wave, the source has to vibrate at the desired frequency. A well-known example is a *harmonic wave*, that is, a sine wave of constant amplitude. Mechanical waves can be either *transverse* or *longitudinal*. If the disturbance is perpendicular to the propagation, the wave is transverse. Some types of transverse waves are referred to as *shear waves*. Shear waves only propagate through solids, because the interactions between molecules in liquids and gases are too weak to propagate shear forces. Longitudinal waves produce disturbances parallel to their travel direction. Sound and shock waves are longitudinal waves, i.e., density variations that can propagate through all phases of matter. Each shock wave causes a compression and expansion (rarefaction) within the medium, changing its density.

Contrary to harmonic acoustic waves, shock waves are sharp discontinuities through which there exists a sudden change in pressure, density, temperature, entropy (a measure of the disorder of a system), and particle velocity (the velocity of the molecules) that result from the sudden release, within a few microseconds, of a large amount of energy in a relatively small space. The passage of a shock wave is an irreversible process and according to the second law of thermodynamics, the entropy increases across the shock front.

Shock waves have been observed in all states of matter (Ben-Dor et al. 2001). The acoustic pressure p (pressure variation due to the wave), the density variation ρ produced by the passage of the wave, and the speed of sound c_0 associated with an

acoustic wave traveling through a medium are related to each other according to the following equation (Cleveland and McAteer 2007):

$$p = \rho c_0^{\,2}. \tag{4.1}$$

The variations in p and ρ actually travel with the wave. For pressure pulses with high amplitude, such as shock waves, the so-called *nonlinear effects* appear (Fig. 4.1). Since the velocity of a wave increases as the pressure rises, wavelets at

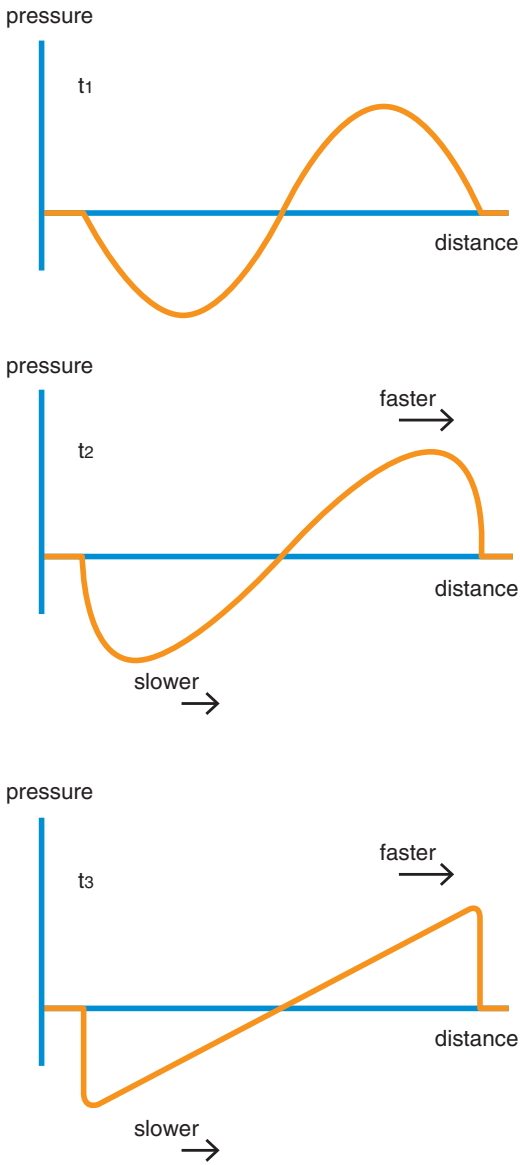


Fig. 4.1 Nonlinear distortion of a pressure wave traveling through a medium from left to right at three instants t_1, t_2, and t_3. Since the crest of the wave is propagating faster than its trough, the waveform gets distorted and the front slope steepens. At t_3, the slope is about to become infinite; however, energy absorption prevents the wave from breaking over (as happens with a water wave). The distance needed by the wave to reach the instant at which the slope is almost infinite is called shock formation distance

low pressure move slower than those at higher pressure. If the initial pressure difference is high enough, the wave crest adopts a sawtooth shape and the pressure pulse transforms into a shock wave, that is, the compression pulse converts into a shock wave when the pressure profile does not pile up any more. At this instant the slope is almost infinite; however, since the absorption also tends towards infinity, the wave does not "break over" as occurs with water waves. On one side, nonlinear effects steepen the shock waves and, on the other side, energy absorption (thermoviscous effects) tends to smoothen them. The slope remains almost infinite until no more energy is delivered from the wave crest. The thickness of the shock wave is inversely proportional to its amplitude and can be considered stationary as long as there is a balance between nonlinear effects and energy absorption. After passing through the focus of a shock wave source, shock waves diverge, reducing their amplitude.

The speed of wave propagation depends on several factors. The most important are the elasticity, the density, and the temperature of the medium. Since the restoring forces between molecules in a solid are higher than in a liquid, waves travel faster in solids than in liquids. They also increase their speed as the temperature rises, because at higher temperature the molecules move faster, colliding with each other more often. The speed of mechanical waves in liquids depends on the *bulk modulus* (Sect. 4.5); that is, on an elastic property of the medium and on the density which is an inertial property of the medium.

Clinical shock wave generators can produce shock waves either immediately after the energy is released by the transducer, as occurs in electrohydraulic and microexplosive sources, or by nonlinear distortion as in self-focusing piezoelectric or electromagnetic shock wave sources where the shock wave develops while the pressure pulse propagates towards the focus (Chap. 5). In electromagnetic sources that use an acoustic lens to focus the energy, the shock front is produced after passing through the lens. All shock wave sources generate pressure fields over a three-dimensional space. These pressure fields can be represented by pressure profiles recorded at several different positions in the field (Fig. 3.3). For biomedical applications, shock waves usually are generated in fluid medium, normally degassed water. Transmission into biologic tissues is achieved by means of open water baths, coupling cushions, or coupling gel.

Pressure measurements demonstrated that shock wave profiles are not affected a lot by traveling through tissue. In vivo waveforms are similar to those recorded in vitro; however, with a positive pressure amplitude reduction of approximately 20–30 % at the focus of the lithotripter (Delius et al. 1987; Cleveland et al. 1998). Contrary to focused shock waves, where the pressure and energy attenuation in soft tissue is relatively low, in the case of radial pressure waves, the pressure and the energy flux density (EFD) decrease rapidly.

As shock waves propagate through the medium, the high frequency components are attenuated more than the low-frequency components. The pressure reduction can be estimated by

$$p = p_0 e^{-bdf^m}, \tag{4.2}$$

where p_0 stands for the initial pressure amplitude, d is the depth in centimeters, b and m are constants, and f is the frequency. Most biological tissues have a value of m between 1 and 2. An advantage of shock waves compared to medical ultrasound is that their frequency spectrum includes lower frequencies (main energy components are around 500 kHz). Because of this, the penetration power of shock waves is relatively high. Nevertheless, the high frequencies associated with the shock front are attenuated more than the low-frequency components of the tensile phase so that the positive pressure peak is attenuated more than the tensile phase of the shock wave. Energy attenuation due to passage of a pressure wave through the membrane of a shock wave source is low; however, as will be explained in Sect. 5.6.8, during clinical practice, wrinkles of the membrane and shock wave reflection at bubbles trapped between the cushion and the patient may affect shock wave transmission significantly (Jain and Shah 2007; Neucks et al. 2008; Bohris et al. 2012).

Several numerical models have been developed to simulate the propagation of shock waves generated by clinical devices (Krimmel 2010). This has been a challenge, because shock waves are nonlinear and not easy to model with finite element techniques. Initially most models were developed to mimic shock wave propagation in the Dornier *HM3* lithotripter. Simulations based on the two-dimensional Khokhlov–Zabolotskaya–Kuznetsov (KZK) equation have been applied successfully to predict pressure fields produced by clinical shock wave sources (Averkiou and Cleveland 1999). The KZK equation accounts for nonlinearity, diffraction, and absorption, and agrees well with pressure measurements. Other authors (Zhou and Zhong 2006) extended the method using data from pressure measurements, introducing the idea of a so-called equivalent reflector. The Euler equations have also been used to model shock wave propagation (Tanguay and Colonius 2001, 2003). Ginter et al. (2002) developed a nonlinear full-wave computational model to provide field predictions and reported results for two shock wave sources: a self-focusing piezoelectric transducer manufactured by Richard Wolf GmbH (Knittlingen, Germany) (Sect. 5.4.1) and a cylindrical electromagnetic transducer with a parabolic reflector provided by Storz Medical AG (Tägerwilen, Switzerland) (Sect. 5.3.2). Comparison between the analytical solutions and the pressure measurements revealed good agreement. Their nonlinear model that included nonlinear steepening and propagation of shock waves was based on the general equations of hydrodynamics for ideal fluids and can be used to study the behavior of therapeutic shock wave sources. Zhang et al. (2009) developed an accurate model by solving the conservation law form of the axisymmetric Euler equations to simulate the propagation of shock waves produced by a piezoelectric extracorporeal lithotripter. Their results confirmed that the location of the focal spot (Sect. 3.4) differs from the geometric focus. Fagnan (2010) studied the propagation of shock waves in ESWT by solving a Lagrangian form of the isentropic Euler equations in the fluid and linear elasticity in the bone using high-resolution finite volume methods. An interesting feature of this simulation is that a three-dimensional system of equations was solved and shear stresses generated within the complex bone geometries could be handled.

4.3 Reflection and Refraction

Shock waves like other compressive waves may undergo *reflection*, *refraction*, *diffraction*, and *scatter* when passing acoustic interfaces at which the acoustic properties change. For the purpose of this book, two relevant cases are shock wave reflection on a rigid wall and the reflection at a free boundary. At boundaries with similar acoustic impedances, such as water and soft tissue only minor effects occur, i.e., underwater shock waves can be coupled into the patient's body with little energy loss because the acoustical properties of water and soft tissue are similar. However, cavities having a low density, as air bubbles, will block shock wave passage.

When a shock wave hits a metallic reflector, an acoustic lens or encounters a gas-filled cavity, a kidney stone, or a bony structure inside the patient's body, part of the wave is reflected and part of it is *refracted*. As the shock wave passes through the boundary, its velocity changes and refraction occurs, changing its direction of propagation. Examples of interfaces with huge differences in the acoustic impedance are soft tissue-urinary stone, or soft tissue-lung cavity boundaries. The large differences in density between air and living tissue are one reason why, for biomedical applications, shock waves are generated in liquid.

The law of geometrical acoustics, which predicts that the angle of incidence of an incoming wave equals its angle of reflection, is valid only for low pressures (Whitham 1959). For underwater shock waves impinging on a metallic reflector, the angle of reflection is larger than the angle of incidence (Müller 1987). This difference grows as the angle of incidence increases. Figure 4.2 shows that at the

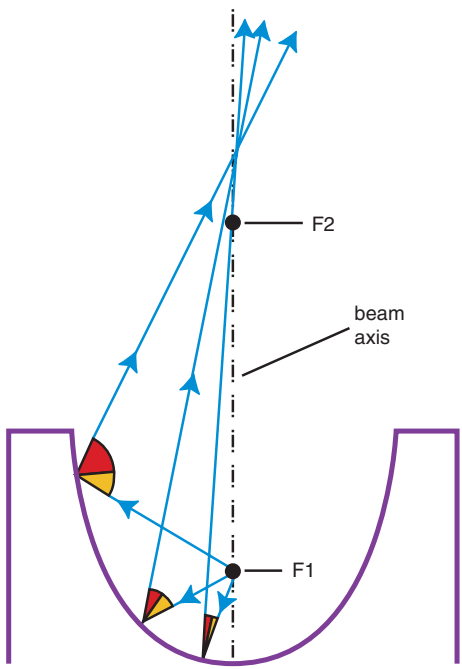


Fig. 4.2 Schematic diagram of an ellipsoidal reflector showing that, for large angles of incidence, the angle of the reflected shock front increases. The rays are perpendicular to the incoming and reflected shock fronts. The differences between angles of incidence and reflection have been exaggerated for clarity

deepest section of the reflector, the angle of incidence is almost equal to the angle of reflection; however, for rays arriving at the upper section of the reflector, the angle of reflection increases, preventing them from reaching *F2*. In most shock wave sources for biomedical applications, this effect is small and is compensated by the fact that the energy density of the focused shock wave near *F2* is higher close to the beam axis. Because of this, in this region the pressure and the velocity increase, flattening the shock front near the axis. This phenomenon shifts the focal region towards the reflector. Waves generated at the lower section of the reflector and propagating along its surface to the upper border may cause significant interference and should be considered when choosing the material and designing the shape of a reflector for an electrohydraulic shock wave generator (Wess 1984).

When a pressure pulse passes from a medium with low *acoustic impedance* (resistance to acoustic conductivity), such as isotonic solution, urine, or tissue, into a medium with high acoustic impedance (kidney stone or bone), the transmitted energy is lower than the incident energy; however, the pressure amplitude of the transmitted wave is higher than that of the incident wave. As expected, kidney stones with high acoustic impedance reflect the incoming shock wave better than stones with lower impedance (Bhatta et al. 1989).

At the boundary between a medium with acoustic impedance Z_1 and a medium with acoustic impedance Z_2, the reflection coefficient R and the transmission coefficient T for acoustic waves are

$$R = \frac{p_r}{p_i} = \frac{Z_2 - Z_1}{Z_2 + Z_1}, \tag{4.3}$$

and

$$T = \frac{p_t}{p_i} = \frac{2Z_2}{Z_2 + Z_1}, \tag{4.4}$$

where p_i, p_r, and p_t are the pressure amplitudes of the incident, reflected, and transmitted waves. These simple equations are valid only for the so-called normal incidence, i.e., if the direction of wave propagation is perpendicular to the interface. In this special case, the intensity reflection coefficient R_I and the intensity transmission coefficient T_I are defined by:

$$R_I = \frac{I_r}{I_i} = \frac{\left(Z_2 - Z_1\right)^2}{\left(Z_2 + Z_1\right)^2}, \tag{4.5}$$

and

$$T_I = \frac{I_t}{I_i} = \frac{4Z_2Z_1}{\left(Z_2 + Z_1\right)^2}, \tag{4.6}$$

where I_i, I_r, and I_t stand for incident, reflected, and transmitted intensity. At the interface, the absolute value of the intensity of the incident wave (I_i) is equal to the sum of the intensity of the transmitted wave I_t and the intensity of the reflected wave I_r. According to Eqs. (4.3)–(4.6), when an acoustic wave travels from a low-impedance to a high-impedance medium ($Z_1 < Z_2$) the pressure amplitude of the transmitted wave is greater than that of the incident wave; however, the transmitted intensity is smaller than that of the incident wave. An example is the boundary between tissue ($Z \approx 1.6 \times 10^6$ kg m^{-2} s^{-1}) and cortical bone, i.e., the outer shell of most bones ($Z \approx 5.9 \times 10^6$ kg m^{-2} s^{-1}). If the wave propagates from a medium with high impedance to a region with lower impedance, the pressure amplitude of the transmitted wave is smaller than that of the incident wave. This occurs, for instance, when a wave exits the rear side of a kidney stone (Z between 2×10^6 and 5×10^6 kg m^{-2} s^{-1}) and enters soft tissue or urine ($Z \approx 1.4 \times 10^6$ kg m^{-2} s^{-1}). Further discussions on shock wave reflection can be found in the literature (Blackstock 2000; Ben-Dor et al. 2001; Eliasson 2007).

Equation (4.4) can also be used to calculate the pressure transmitted through a test vial. This is important for in vitro shock wave exposure of cell suspensions (Chap. 7). Furthermore, the design of test vials for in vitro experiments is important to mimic in vivo conditions to better understand how the stimuli of pressure waves is translated into biological cell signals (Holfeld et al. 2014a). In general, the pressure p_t transmitted through an interface equals the incident pressure p_i multiplied by the transmission coefficient T. For a test vial exposed to underwater shock waves, the wave passes through two interfaces: the water (W)–container (C) interface and the container–water (cell suspension) interface. The pressure transmitted through both interfaces can be obtained using the following equation (Dietz-Laursonn et al. 2016):

$$p_t = p_i \frac{4 Z_W Z_C}{\left(Z_W + Z_C\right)^2}. \tag{4.7}$$

4.4 Diffraction

A sound wave that is directed towards an aperture with a size that is equal to or smaller than its wavelength may emerge in different directions. This phenomenon, called *diffraction* may appear with light waves too; however, diffraction of sound is experienced more frequently, because the wavelength of sound is comparable in size to many objects encountered in our daily life. Sound waves also have the capacity to bend over corners. Diffraction produces cigar-shaped focal volumes and is one of the causes that prevent shock waves from being focused to a point (Cleveland and McAteer 2007).

Considering diffraction effects when designing shock wave sources may have advantages. For instance, modifying the diffraction wave at the reflector aperture

of an electrohydraulic lithotripter (Sect. 5.2.1) changes the pressure waveform that reaches the focal zone. Zhou (2012) fitted an extension on the outside of a Dornier *HM3* reflector to disturb the diffraction wave (Fig. 4.3). The device consisted of eight trapezoidal segments made out of undulated foam attached to a supporting Lucite plate. Foam was chosen because it is an acoustic absorbent material. Pressure measurements performed with a light spot hydrophone (Sect. 3.6) revealed that the peak-positive pressure (p^+) and the −6 dB focal zone did not vary; however, the duration of the tensile wave was shortened significantly after installing the edge extender. As a consequence, shock wave-induced cavitation was reduced. This was verified using passive cavitation detection. Shock wave-induced damage to blood vessel phantoms made of cellulose hollow fiber, with and without the extension, was compared. Approximately 30 shock waves generated at a discharge voltage of 20 kV (80 nF capacitor) were needed to rupture blood vessel phantoms with the non-modified reflector. With the edge extender, no damage could be produced after up to 300 shock waves using the same voltage. In vitro kidney stone phantom fragmentation efficiency was comparable with and without the edge extender.

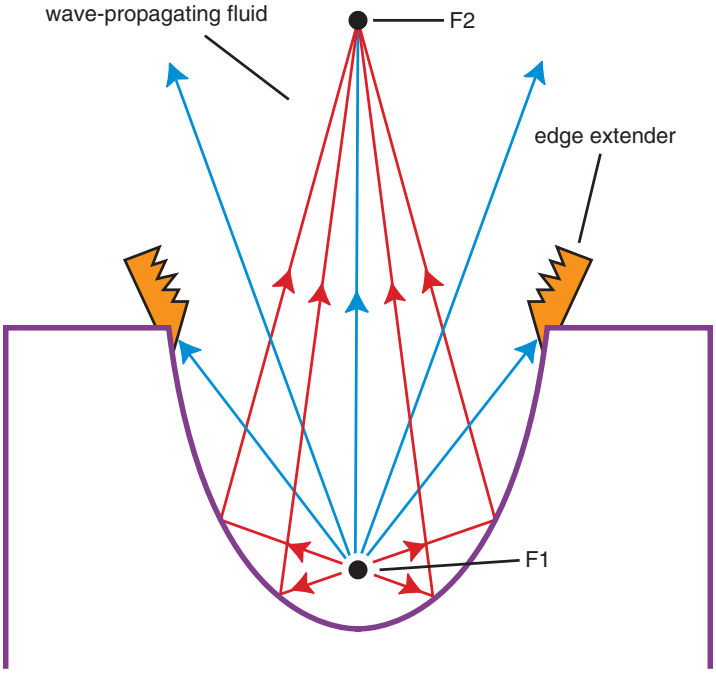


Fig. 4.3 Rays indicating the direction of focused shock waves in an electrohydraulic shock wave generator with edge extenders made out of an acoustic absorbent material and fitted on the reflector of a Dornier *HM3* shock wave generator as proposed by Zhou (2012). The design consisted of eight trapezoidal segments

4.5 Compression, Tear, and Shear Forces

All materials are elastic to some extent and an external force is needed to change their shape; however, internal forces will oppose deformation. During brittle fracture an object absorbs only little energy before failure. Contrary to this, a ductile fracture involves *plastic deformation*. For instance, gallstones are relatively ductile and have the capacity to absorb shock wave energy through plastic deformation. This is one of the reasons why SWL has been less effective to treat gallstones compared to kidney stones (Maglinte et al. 1991).

When studying the deformation of solids, two important concepts are *stress*, that is, the force applied to an object per unit cross-sectional area, and *strain*, which is a quantity that gives information on the deformation achieved after applying stress. If the stress on an object exceeds a certain threshold, it will fracture; however, if the applied stress is not too large, then strain is proportional to stress. The ratio of stress to strain is referred to as the *elastic modulus* and depends on the properties of the material and on the way stress is applied to it. The mechanical resistance of a solid object to a change in its length is measured by the *Young's modulus*, that is, the ratio of tensile stress to tensile strain. The opposition of the object to shifting of planes inside it is determined by the so-called *shear modulus*, defined as the ratio of shear stress to shear strain. Finally, its resistance to a change in volume is measured by the *bulk modulus*, i.e., volume stress divided by volume strain. The speed of a mechanical wave propagating through a solid object is influenced by the bulk modulus. Sometimes the *compressibility*, that is, the reciprocal of the bulk modulus, is used instead of the bulk modulus.

The variability of SWL outcomes for urinary stones is high. One reason for this is that stone fragmentation depends on the size of the stone, its orientation, shape, chemical composition, and internal structure. Renal calculi have a huge variety of shapes and properties (Singh and Agarwal 1990). They may be composed of uric acid, cystine calcium, oxalate monohydrate and dihydrate, calcium monohydrogen phosphate, and magnesium ammonium phosphate hydrogen (MAPH). Each urinary stone has a unique shape, composition, and crystalline structure. Stones containing calcium combined with either phosphate or oxalate are common. Uric acid and cystine stones appear less frequently. Some calculi are formed from crystals that separate from urine and are joined together by organic deposits. They build up on the inner surfaces of the kidney and generally are weak. Stones with a heterogeneous and laminated structure are more fragile than homogeneous calculi and struvite or infection stones are related to infections in the urinary tract.

Because the physical and chemical properties of urinary stones vary a lot (Fig. 4.4), well standardized kidney stone phantoms have played an important role for in vitro and in vivo research (Fig. 4.5). More than one type of stone model should be used to characterize the fragmentation efficiency of a specific shock wave lithotripter. Different materials such as chalk, gypsum, Vel-mix stone (Kerr Division of Syborn Corp., Romulus, MI, USA), and various ceramic materials have been used to manufacture artificial stones (Vakil 1991; Favela et al. 2005; McAteer et al. 2005b;

Fig. 4.4 Photograph of urinary stones, showing their variety in shape and composition. (Photograph: A. Sánchez)

Fig. 4.5 Photograph of three (30×30×14.3 mm) AST 110 stone models (High Medical Technologies, Kreuzlingen, Switzerland), before (*left*) and after exposure to 500 underwater shock waves generated with an electrohydraulic (*center*) and a piezoelectric (*right*) shock wave source

Gutiérrez-Aceves et al. 2006; Hurtado et al. 2007; Gutiérrez et al. 2008; Nyame et al. 2015). Stone phantoms consisting of uric acid, struvite cystine, calcium oxalate, brushite, and apatite, with a dense core surrounded by a homogeneous matrix, have also been manufactured and tested for their attenuation numbers in spiral computed tomography (CT) (Bachmann et al. 2000). Nyame and colleagues (2015) described models to test shock wave sources for SWL, highlighting the different fabrication methodologies.

During in vitro stone fragmentation it has to be considered that not only stone structure, but also stone orientation affects the mechanism of failure (Cleveland and van Cauwelaert 2005). In the early days of SWL, p^+ was considered as the most important parameter for stone disintegration. The amplitude of the positive pressure pulse transmitted into the stone was correlated with treatment outcomes; however, in vitro experiments revealed that other parameters have a greater influence on stone disintegration. According to an article published by Whelan and Finlayson, kidney stones resist compressions of up to 18 MPa (Whelan and Finlayson 1988). Wang et al. (2002c) reported that the compressive strength of urinary stones ranges from approximately 3.2–6.2 MPa.

Even if water only transmits longitudinal waves, both longitudinal and shear waves have been observed inside stone phantoms during in vitro fragmentation.

At the beginning of SWL, pressure variations inside the stone produce tensile and shear stress. Shear forces tend to separate layers of the urinary stone. The first fissures appear where the stress exceeds a certain limit. Compression and tension of urinary stones causes growth of microscopic flaws and loss of cohesiveness (Lokhandwalla and Sturtevant 2000). Reflections of shock waves inside the stone also contribute to produce small fissures. As these fissures become filled with liquid (urine), cavitation (Sect. 4.7) begins to contribute to stone disintegration from the inside (Sass et al. 1991). Stress wave-induced fracture occurs mainly at the beginning of the treatment while cavitation contributes during the remaining phase (Zhu et al. 2002).

Elastic wave propagation and crack initiation in kidney stones during SWL has been studied using numerical simulations and high-speed photoelasticity (Cleveland and Sapozhnikov 2005; Sapozhnikov et al. 2007; Wijerathne et al. 2010). Xi and Zhong (2001) published images of stress waves observed in epoxy samples during shock wave exposure and analyzed crack patterns in plaster of Paris stone phantoms. They concluded that shear waves are responsible for the formation of fissures. Kredrinskii (1997) used a mathematical model to show that stone comminution can be achieved when focusing tensile instead of compressive waves and Cathignol (1998) reported that a tensile wave followed by a positive pressure pulse is more efficient in fracturing kidney stones than conventional shock waves. Lewin et al. (1990), Bailey (1997a), and Carnell et al. (1997) also studied the effects of a negative pressure phase followed by a positive waveform (*pressure-release shock waves*). Interestingly Evan et al. (2002) reported that this type of shock waves produce less tissue damage.

4.6 Hopkinson Effect

Because most urinary stones are brittle materials, they withstand compression better than tension. Fracture may occur by conversion of the initially compressive shock pulse into a reflected tensile wave inside the stone. If a shock wave impinges on an acoustically *soft interface*, i.e., if it propagates from a medium with high impedance (stone) to a region with lower impedance (urine or soft tissue), a large amount of energy is reflected at the boundary between both media. The reflected part of the wave becomes tensile, i.e., a high-amplitude negative pressure pulse travels in the opposite direction to that of the original incoming shock wave (Fig. 4.6). According to the laws of acoustics, if the acoustic impedance of the second medium is lower than that of the first medium, a positive pressure pulse is reflected as negative. Incident and reflected waves add, and a fracture is produced at the site where the net effect of the two waves is sufficiently tensile to induce a cleavage plane, i.e., nucleation and formation of microcracks occur that can coalesce to result in fragmentation. At normal incidence on a flat acoustically soft interface (as may occur in kidney stone phantoms), the failure surface is orthogonal to the shock wave

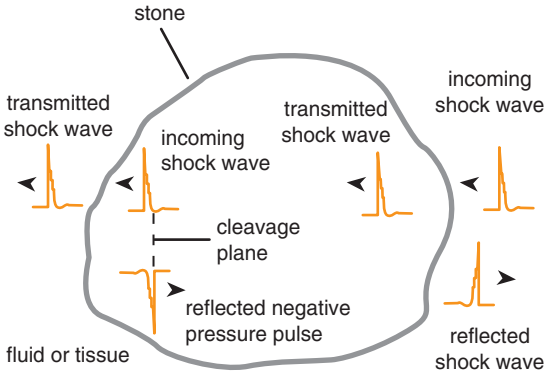


Fig. 4.6 Schematic diagram representing spallation (Hopkinson effect) of urinary calculi during shock wave exposure. A cleavage plane is produced close to the distal side of the stone by superposition of the incoming and the reflected wave. In a real scenario, the pressure waveforms vary in shape and amplitude

propagation. This phenomenon is referred to as *spallation* or *Hopkinson effect* (Hopkinson 1914; Häusler 1985; Whelan and Finlayson 1988; Delius et al. 1988c; Xi and Zhong 2001; Gama et al. 2004; Sapozhnikov et al. 2007). The Hopkinson effect is considered to be a significant fragmentation mechanism at the beginning of SWL and may also occur at internal interfaces, that is, at tiny cracks and fluid-filled cavities inside the stone. Figure 4.7 shows the photograph of a cylindrical kidney stone model before and after shock wave exposure. Typical spalling can be seen in Fig. 4.7b on the rear side (shock wave-exit side) of the stone.

There is a minimal stone size for spall to occur (Xi and Zhong 2001). Once the fragments are smaller than this size, other mechanisms such as acoustic cavitation (Sect. 4.7) continue to pulverize them. The distance between the distal surface of the stone and the spall depends on its density and on the pressure waveform. Hard stones will result in larger fragments. Smaller fragments are produced by shock waves with a short duration. Cleveland et al. (2002) reported that when fragments become 3–4 mm in size, spalling is no longer effective; however, this also depends on the shape of the stone fragment and on the angle of incidence of the shock wave. High peak-positive pressure generates strong spalling effects. As will be explained in Sect. 4.13, bony structures are more resistant to spalling because they are not as brittle as urinary calculi.

4.7 Acoustic Cavitation

Bubbles may be formed in liquids by boiling or *cavitation*. Cavitation is defined as the process of rupturing a liquid by decreasing its pressure below a threshold without significantly changing the temperature, while boiling is the process of rupturing a liquid by increasing its temperature without significantly changing the pressure. Cavitation can be produced due to high streaming velocities. In most situations, a large number of bubbles grow and collapse.

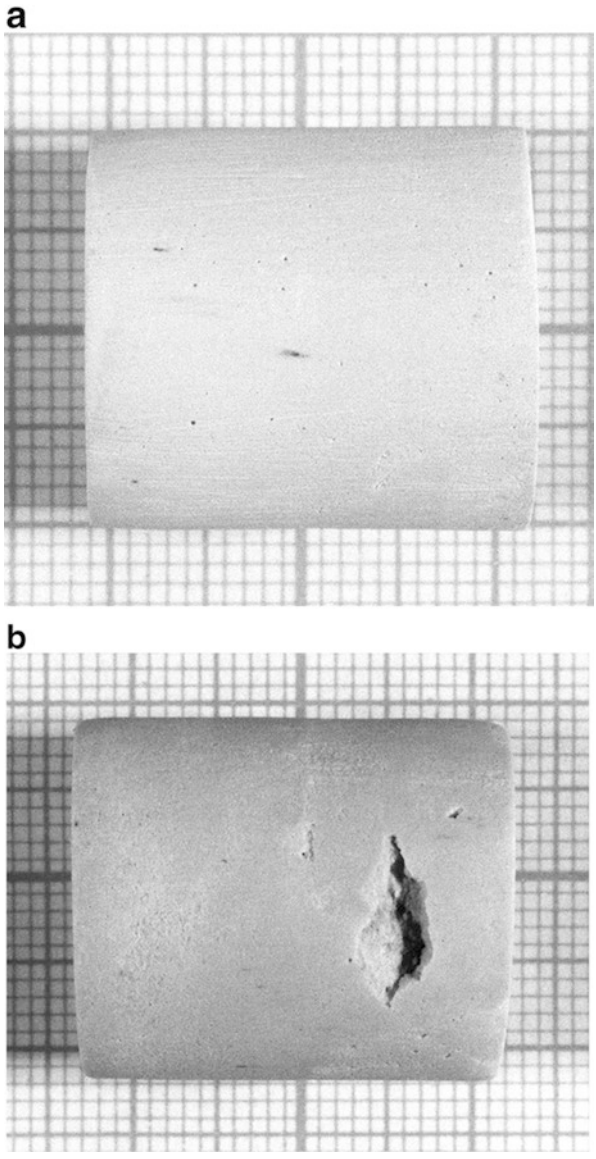


Fig. 4.7 **(a)** Photograph of an intact kidney stone phantom used to study in vitro fragmentation mechanisms and to evaluate the performance of shock wave sources. **(b)** Photograph of spallation at the shock wave-exit side of a stone phantom as shown in (**a**) after in vitro exposure to a few underwater shock waves

Acoustic cavitation is the growth and collapse of bubbles in a liquid driven by an acoustic wave. The negative pressure phase generates bubble growth, while the hydrostatic pressure and the positive pressure of the wave cause an inertial collapse.

Transient cavitation is often considered as a problem. It can erode ship propellers, hydraulic equipment, fuel injection nozzles, valves, and spillways (Blake and Gibson 1987); however, beneficial uses such as ultrasonic cleaning, drug delivery into cells, and histotripsy are also known. In cavitation histotripsy, short pressure

pulses maintain a cloud of tiny bubbles at the transducer focus to disintegrate tissue into submicron-size fragments (Xu et al. 2004; Parsons et al. 2006a; Maxwell et al. 2012; Simon et al. 2012; Vlaisavljevich et al. 2014). The so-called *stable cavitation*, i.e., the oscillation of a gas bubble in an acoustic field inside a fluid-filled flask (Gaitan et al. 1992; Leighton 1994; Brennen 1995), does not occur in biomedical applications. In this case, a gas bubble is levitated in a degassed fluid and oscillates in the antinode of a standing wave field. At each collapse the bubble radiates a short flash of light and a pressure pulse. Contrary to transient cavitation the phenomenon is highly reproducible, the bubble does not disintegrate and the process is repeated in a synchronous fashion.

Because of the existence of nucleation sites within most liquids, cavitation thresholds are normally much smaller than predicted by theory. In biomedical applications, cavitation generally does not occur because liquid molecules are broken apart, but because the fluid contains nucleation sites, i.e., spots where cavitation can occur easily. Any bubble immersed in a fluid will grow if the tension is larger than the opposing static pressure and the surface tension forces. Acoustic cavitation may take place for both radial pressure waves and focused shock waves. The phenomenon has been intensively studied and reported to contribute to stone fragmentation both in vitro and in vivo, and to enhanced delivery of drugs and genetic materials. It is also implicated in desired and non-desired effects on tissue, cells, and microorganisms (Crum 1979, 1988, Crum and Fowlkers 1986; Coleman et al. 1987a; Fischer et al. 1988; Vogel and Lauterborn 1988; Church 1989; Delius et al. 1990a, 1998; Field 1991; Choi et al. 1993; Vakil and Everbach 1993; Rink et al. 1994; Brennen 1995; Delacrétaz et al. 1995; Wiksell and Kinn 1995; Leighton 1994; Bailey 1997b; Lifshitz et al. 1997; Zhong et al. 1997b, 1999a; Evan et al. 1998a; Williams et al. 1999; Young 1999; Zhu and Zhong 1999; Carstensen et al. 2000; Akhatov et al. 2001; Sokolov et al. 2001; Zhu et al. 2002; Pishchalnikov et al. 2003; Arora et al. 2005; Bailey et al. 2005; Chitnis and Cleveland 2006; Iloreta et al. 2007; Klaseboer et al. 2007; Tu et al. 2007; Johnsen and Colonius 2008; Chen et al. 2010; Loske 2010; Kreider et al. 2011b; Zhong 2013; Angstman et al. 2015; Császár et al. 2015; Lukes et al. 2016; Wan et al. 2015).

Preexisting bubbles in the vicinity of the focus of a shock wave source get compressed as the positive pressure component of the shock wave arrives. During this fast compression, referred to as *forced collapse*, the pressure inside the bubbles increases drastically. After shock wave passage, the extremely high pressure inside the compressed bubbles and the trailing tensile phase of the shock wave trigger a fast bubble growth, forcing the liquid surrounding each bubble outward. The rebound of each bubble leads to the emission of a strong pressure transient into the surrounding liquid, which can develop into a shock front. As the volume of the bubbles increases, the pressure inside them decreases until they suffer a violent *inertial collapse*. Under certain circumstances, high-speed fluid microjets and secondary shock waves are generated during collapse. Bubbles induced by shock waves as used in biomedical applications expand and disintegrate in a violent collapse after approximately 200–700 μs (Kodama and Tomita 2000; Evan et al. 2002; Bailey et al. 2005). High-speed cameras have been used to analyze bubble dynamics; however, the lack

of knowledge on the exact spot of their appearance complicates recording. Liquid jet emission during bubble collapse was suggested in an article published in the 1940s (Kornfeld and Suvorov 1944); however, it seems that the first to study the formation of microjets inside an underwater bubble collapsing next to a solid boundary were Naudé and Ellis (1961).

The larger a bubble grows, the more violent its collapse will be. The dynamics of a bubble depends on several factors, such as the driving pressure waveform, the content of dissolved gases, the vapor pressure, the viscosity, the surface tension, the temperature of the liquid, and the existence of microbubbles of gas or microscopic solid kernels that act as cavitation nuclei. The occurrence of cavitation reduces as the viscosity of the fluid rises. At higher temperatures, the viscosity reduces and bubbles form more easily; however, bubble collapse is less violent, because of the higher vapor pressure inside the bubble. Bubble collapse also depends on the proximity to solid boundaries (Church 1989). In tap water the typical radius of an air bubble is approximately 3 μm and in urine nuclei of about 1 μm to 1 mm may be present. Figure 4.8 shows the dynamics of a single spherical air bubble immersed in water, subjected to a typical lithotripter shock wave, modeled by the Gilmore–Akulichev equation (de Icaza-Herrera et al. 2015).

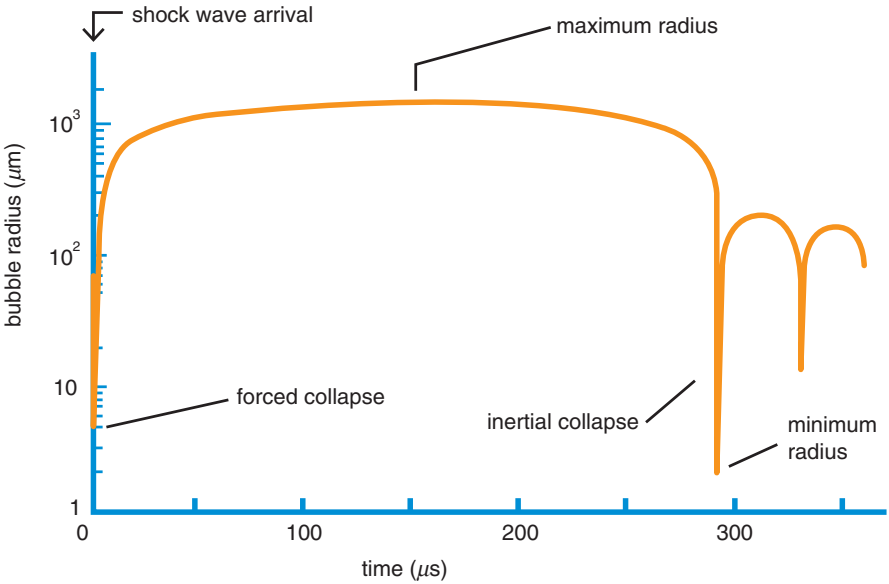


Fig. 4.8 Graph of a numerical simulation showing the variation of the radius of an air bubble in water (initial radius $R_0 = 0.07$ mm) exposed to a lithotripter shock wave ($p^+ = 100$ MPa). An abrupt forced bubble collapse is followed by an expansion and a second collapse. The second collapse occurred approximately 290 μs after arrival of the shock wave at $t = 0$. The bubble rebounds several times (not shown completely) until reaching equilibrium. (Courtesy of M. de Icaza-Herrera)

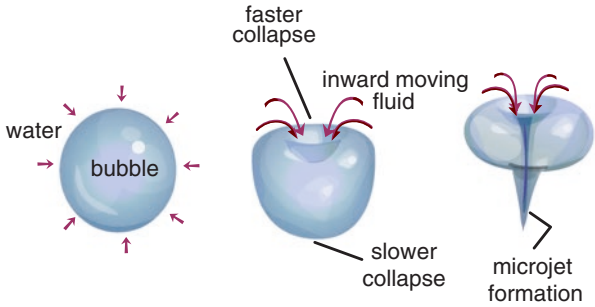


Fig. 4.9 Schematic of a collapsing microbubble in water and microjet emission after shock wave passage. Because an interface (not shown) is close to the bottom of the bubble, the bubble involutes from the top and develops a funnel-shaped protrusion and a fluid microjet in the direction of the boundary. Adapted from Wess (2004)

If the bubble expands close to a rigid boundary such as a urinary stone, the flow will change its radial direction, moving outwards along the boundary. As the bubble starts to collapse, the water moving in between the boundary and the bubble is slower than the water on the opposite side of the bubble, so that the pressure drop next to the boundary is faster because there is less water to fill the space initially occupied by the bubble. This pressure difference moves the bubble towards the boundary. Because of the flow drag caused by the boundary, the collapse is asymmetrical (Fig. 4.9). The fluid on one side of the bubble accelerates inward more rapidly than on the opposite side, resulting in the development of a high-speed microjet of fluid that burrows through the bubble towards the boundary (Lauterborn and Bolle 1975; Shima and Nakajima 1977; Crum 1979, 1988; Blake and Gibson 1987; Coleman et al. 1987a; Zhong et al. 1993; Blake et al. 1997; Lauterborn and Ohl 1998; Philipp and Lauterborn 1998; Brujan et al. 2002, 2008; Ohl and Ikink 2003; Klaseboer et al. 2007; Sapozhnikov et al. 2007).

The collision between the inward-moving bubble wall and the microjet is so violent that it generates a secondary shock wave, which may reach a pressure of up to 300 MPa. This shock wave can contribute to calculi disintegration during SWL; however, its effects are confined to small distances (Brujan et al. 2008). The radius of the fluid jet is typically about one tenth of the bubble radius (Kodama and Takayama 1998). Interesting details of shock wave passage through water are shown in Fig. 4.10. Positive pressure gradients are displayed in red (*eBook*), while the negative phase appears green. The shock wave traveled from the bottom to the top of the image, generating bubble growth and collapse.

Matula et al. (2002b) performed direct measurements of individual bubble oscillations after shock wave passage using light-scattering techniques. Their numerical simulations agreed well with the observations, provided that vapor trapping was considered. Vapor trapping occurs because the collapse becomes so rapid that there is insufficient time for vapor inside the bubble to escape. Under certain circumstances,

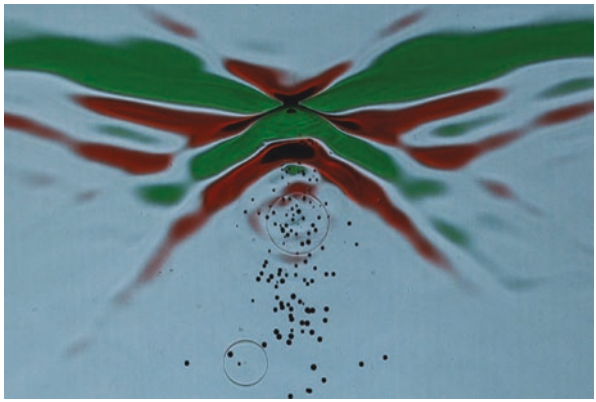


Fig. 4.10 Details of a focused shock wave field in water, showing generation of cavitation bubbles (*black dots*) in the negative pressure area. Bubbles grow and collapse, radiating spherical shock waves. Technique: color-schlieren optics displaying positive pressure gradients in red und negative pressure gradients in green (*eBook*) (Photograph: O. Wess and J. Mayer, Storz Medical AG, Tägerwilen, Switzerland)

vapor trapping seems to prevent the bubble from disintegration upon collapse. According to their results, the formation of hydroxyl radicals is related to the amount of water vapor trapped in the bubble.

Acoustic emissions due to lithotripsy-induced bubble collapse close to kidney stone phantoms have been measured by Chitnis and Cleveland (2006). The authors concluded that at the stone surface, microbubble collapse produces peak pressures of the same order as the incident shock wave. Philipp et al. (1993) used high-speed photography to study the formation of microjets during underwater shock wave-induced bubble collapse and recorded fluid jets of more than 700 m/s at the focus of the shock wave source. Their experimental results corresponded well with calculations done using the Gilmore model. Microjets may strike neighboring cavitation bubbles, causing them to collapse even faster. Depending on the shock wave rate, nuclei seeded by cavitation from a previous shock wave may still exist as the next shock wave arrives. Figure 4.11 shows pitting produced by shock wave-induced fluid microjets on a cylindrical kidney stone phantom.

Cavitation is considered to be the most important fragmentation mechanism to comminute urinary stones that are very resistant to compression and shear forces, such as cystine and calcium hydrogen phosphate dihydrate or brushite stones (Wang et al. 1993). Figure 4.5 shows a photograph of the crater produced to rectangular standardized kidney stone phantoms after in vitro underwater exposure to the same number of shock waves generated with an electrohydraulic and a piezoelectric shock wave source (Chap. 5). Pits produced by cavitation are evident on both shock wave treated stones; however, the diameters and depths of the craters are different.

During a cavitation event the energy concentration into such a small volume produces an enormous energy density that can yield free radicals, arising from temperatures exceeding 5000 degrees Kelvin (Morgan et al. 1988). These spots,

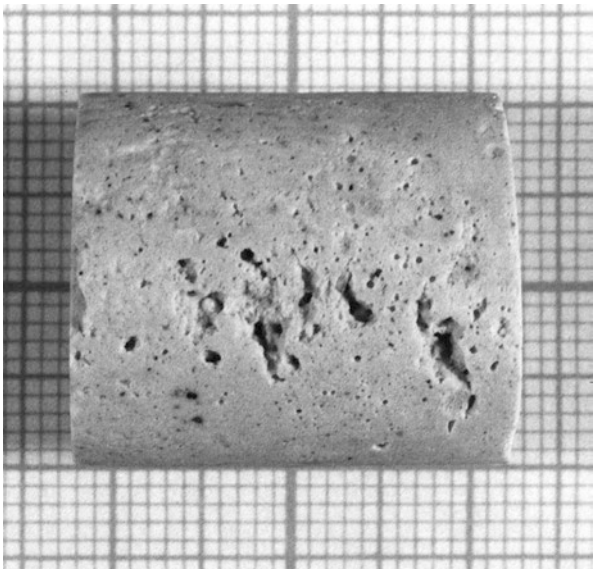


Fig. 4.11 Photograph of the shock wave-entrance side of an artificial stone model as shown in Fig. 4.7a, showing pitting caused by acoustic cavitation after in vitro exposure to underwater shock waves

characterized by very high temperatures and pressures in a small space, normally do not affect the bulk temperature. The oxygen-free radicals may inactivate enzymes, degrade DNA, and produce cell apoptosis. Choi and colleagues (1993) reported that, at a distance of approximately 2 mm from bubble collapse, the emitted pressure has a magnitude of about 100 MPa.

Secondary shock waves induced by bubble collapse may be responsible for some phenomena occurring not only during SWL but also ESWT. The fact that suppression of acoustic cavitation by increasing the static pressure or the viscosity, or by modifying the pressure profile, significantly reduces stone fragmentation efficiency, demonstrates the importance of this phenomenon during SWL (Bailey 1997b; Delius 1997; Vakil and Everbach 1993; Xi and Zhong 2000; Pearle 2002). At increased hydrostatic pressure, cavitation is reduced because bubbles cannot expand freely. This was demonstrated in vitro by a reduction of the lysis of red blood cells in suspension by application of excess hydrostatic pressure (Williams Jr et al. 2002).

Bubbles may collapse asymmetrically even in the absence of a boundary. In this scenario, the fluid microjets are emitted along the direction of shock wave propagation; however, only bubbles very close to an object are capable of producing damage to it. This phenomenon is supposed to be responsible for in vitro cell membrane permeabilization (Sects. 7.4, 7.5, and 7.6).

Because the phenomena by which bubble collapse induces injury and comminutes stones are different, in principle it is possible to increase stone comminution and reduce tissue injury at the same time. Cavitation-induced microjets and secondary shock waves are believed to contribute to calculi disintegration during SWL, while the rupture of small blood vessel is caused by the intraluminal expansion of cavitation bubbles (Zhong and Zhou 2001; Zhong et al. 2001). Microjets are not

likely to be responsible for injury to small blood vessels, because asymmetric bubble collapse with microjet emission may not occur if the bubble size is too small (Philipp et al. 1993). As will be described in Sect. 5.5.3, Zhou et al. (2004b) proposed the use of modified lithotripter pressure waveforms to suppress intraluminal bubble expansion without reducing stone comminution.

Urinary stones confined in small spaces without fluid surrounding them are more difficult to pulverize, because bubble expansion is constrained by the surrounding tissue (Zhong et al. 1998a). Furthermore, soft tissue contains fewer cavitation nuclei than body fluids (Carstensen et al. 2000; Zhong et al. 2001; Freund 2008). For cavitation to damage a stone, at least part of its surface has to be exposed to fluid (urine, blood, physiological saline). During SWL it is desirable to create a fluid-filled "expansion chamber" surrounding the stone.

Evidence of cavitation within tissue has been obtained using focused passive receivers and B-mode ultrasound (Coleman et al. 1996; Zhong et al. 1997a, b). Bailey and colleagues (2005) reported cavitation during in vivo shock wave treatment in the renal parenchyma. The authors detected cavitation within the urine in the kidney after fewer than 100 shock waves. They also reported that the number of bubbles increases over the course of the treatment and that in tissue about ten times as many shock waves are needed for cavitation to be observed. It seems reasonable to believe that since these experiments were conducted in animals without kidney stones, the presence of stone fragments would nucleate more bubbles. Furthermore, miniature gas bubbles may appear on suspended particles. When exposed to shock waves, these microbubbles can act as cavitation nuclei. Borkent et al. (2007) showed that hydrophobic and corrugated polymer particles enhance cavitation, while smooth and hydrophilic particles reduce cavitation activity.

At the beginning of an SWL treatment, only few bubbles arise from preexisting cavitation nuclei. As the treatment progresses, stone fragments and remains of cavitation bubbles provide more and more cavitation nuclei. Cleveland et al. (2000b) used the so-called *passive cavitation detection* (PCD) to study shock wave-induced bubble growth and collapse. As explained in Sect. 3.6, the technique is based on recording emissions from oscillating bubbles immersed in a fluid by means of focused transducers. Tu et al. (2007) studied in vitro and in vivo shock wave-induced cavitation using B-mode ultrasound. Bubble dynamics after shock wave passage was analyzed for different energies and shock wave rates. As expected, larger echogenic regions, i.e., enhanced bubble activity, were observed with higher shock wave energy or faster shock wave rate.

Several numerical methods have been proposed to simulate the dynamics of bubble collapse in the field generated by shock wave sources for biomedical applications (Church 1989; Ding and Gracewski 1996; Zhu and Zhong 1999; Tanguay and Colonius 2001, 2003; Sapozhnikov et al. 2002; Arora et al. 2005; Brujan et al. 2005, 2011; Yang and Church 2005; Klaseboer and Khoo 2006; Liebler 2006; Klaseboer et al. 2007; Turangan et al. 2008; Johnsen and Colonius 2009; Canseco et al. 2011; Kreider et al. 2011a). Two popular equations to study the dynamics of bubbles subjected to shock waves as used in biomedical applications are the Rayleigh–Plesset and the

Gilmore equation (Plesset 1949; Gilmore 1952; Plesset and Prosperetti 1977; Prosperetti 1984). The Rayleigh–Plesset equation describes the dynamics of a free gas bubble in an incompressible fluid. A second-order ordinary differential equation for the radius of a spherically symmetric bubble is obtained by combining the conservation equations for mass and momentum in the liquid and spatially integrating over the radial coordinate. The equation has been extended to study bubbles in a viscoelastic material and also to analyze the dynamics of bubbles in liquids surrounded by a viscoelastic material (Allen and Roy 2000; Emelianov et al. 2004; Yang and Church 2005; Church and Yang 2006). A concern could be that the equation considers the ideal case of a bubble immersed in an incompressible fluid exposed to a spatially uniform pressure. Nevertheless, the Rayleigh theory has been used successfully to study bubble dynamics after lithotripter shock wave passage, because in most cases the stone is smaller than the focal region of the shock wave source (Howle et al. 1998).

An advantage of the Gilmore equation is that, contrary to the Rayleigh–Plesset equation, it considers the compressibility of the liquid surrounding the bubble and performs very well simulating inertial collapses (Prosperetti and Lezzi 1986). The model was originally developed to study scenarios different from biomedicine such as underwater explosions (Gilmore 1952). Its main assumptions are that the bubble radius is smaller than the wavelength of the pressure waveform, that the bubble always remains spherical, and that the fluid surrounding the bubble is isentropic. Gas diffusion out of and into the bubble can also be considered in the model. Church (1989) successfully used the Gilmore–Akulichev formulation to study the dynamics of underwater bubbles subjected to shock waves. The model predicts that the radial response of a single spherical air bubble to an underwater shock wave as the one described by Eq. (3.3) is given by (Church 1989; Choi et al. 1993):

$$R\left(1-\frac{U}{C}\right)\frac{dU}{dt}+\frac{3}{2}\left(1-\frac{U}{3C}\right)U^2=H\left(1+\frac{U}{C}\right)+\frac{RU}{C}\left(1-\frac{U}{C}\right)\frac{dH}{dR}. \tag{4.8}$$

In this equation R is the bubble radius, U is the bubble wall velocity, and C is the speed of sound at the bubble wall, given by

$$C=\sqrt{C_l^2+6H}, \tag{4.9}$$

where $C_l = 1509.7$ m/s and $H = H(P)$ is the enthalpy of the liquid, obtained using the equation of Tait. The enthalpy is a so-called *state function*, defined as the internal energy of the system plus the product of the pressure and the volume of the system. In this case H can be calculated as:

$$H(P)=\int_{P_\infty}^{P}\frac{dP}{\rho}, \tag{4.10}$$

where P_∞ is the "undisturbed pressure," and P and ρ are the time-varying pressure and density of the liquid. As an example, the Gilmore–Akulichev model predicts that a bubble exposed to a compression pulse of 50 MPa with a rise time of 40 ns, followed by a pressure trough of –10 MPa, will collapse in about 20 ns. This collapse is followed by an explosive expansion, increasing the bubble radius from about 3 μm to 1 mm until a second, more violent collapse. Gas diffusion from the water into the bubble occurs before the second collapse (Leighton 1994).

The lack of symmetry complicates the theoretical analysis of bubble collapse after shock wave passage. Interestingly, multiple shock wave emissions and the formation of a second jet (counterjet), directed in the opposite direction of the main microjet, have been reported as a consequence of the collapse of a cavitation bubble (Lauterborn and Ohl 1998). Johnsen and Colonius (2006) published the results of numerical simulations that considered pressure waves generated by non-spherical bubble implosions in liquids. Two years later, the same authors reported a systematic study of bubble dynamics and damage potential associated with shock wave-induced collapse (Johnsen and Colonius 2008).

Many published studies deal with the behavior of a single bubble; however, multiple bubbles are generally present and their dynamics is strongly influenced by complex interactions between them. Arora et al. (2007) reported that if microbubble concentration in a lithotripter field grows from approximately 40–400 nuclei per milliliter, the bubble lifetime increases by about 50 μs. The interaction between two microbubbles and their fluid jet formations have been studied theoretically and experimentally by Lauterborn and Kurz (2010), as well as by Yuan et al. (2011). If the bubbles are generated in-phase, their interaction is similar to the dynamics of a single bubble oscillating close to a rigid wall. However if they oscillate out-of-phase, axial jets are emitted in opposite directions.

Using numerical simulations, pressure measurements, shadowgraph imaging, and passive cavitation detection, as well as extensive in vitro and in vivo experiments, many authors have demonstrated the potential of manipulating waveforms to control shock wave-induced cavitation (Delius and Brendel 1988; Ding and Gracewski 1994; Loske and Prieto 1996, 2001; Zhong et al. 1997a, b; Prieto and Loske 1999; Sokolov et al. 2001, 2003; Zhong and Zhou 2001; Loske et al. 2002b, c, 2004b, 2005; Sankin et al. 2005; Tham et al. 2007; Canseco et al. 2011; de Icaza-Herrera et al. 2015; Lukes et al. 2016). It has been demonstrated that bubble collapse and microjet emission can be significantly enhanced if a second shock wave arrives shortly before the bubbles generated by the previous shock wave start to collapse (Bailey 1997b). The optimal delay between the two shock waves (called *tandem* shock waves) depends on several factors such as the properties of the fluid and the pressure profile. Furthermore, because acoustic cavitation is a multi-bubble phenomenon, the optimal delay may not be easy to determine. Numerical analysis revealed that the second shock wave can have smaller amplitude than the first (bubble-generating) shock wave and still be effective (Bailey 1997b; Canseco et al. 2011). In general, tandem shock waves are defined as two consecutive shock waves, generated within a time delay of approximately 10–900 μs.

Tissue damage could be a concern when using tandem shock wave sources; however, as mentioned above, bubble expansion in vivo is constrained by the tissue and most mammalian tissue has few cavitation nuclei (Zhong et al. 1998a, 2001; Carstensen et al. 2000; Sokolov et al. 2003; Handa et al. 2007; Freund 2008). By properly adjusting the delay, tandem shock waves may improve stone fragmentation, as well as reduce treatment time and tissue damage (Fernández et al. 2009b). Several authors have proposed different solutions to take advantage of shock wave-induced cavitation and introduce tandem SWL into clinical practice, such as the use of composite and bifocal reflectors for electrohydraulic shock wave sources (Loske and Prieto 1996, 2001; Bailey 1997b; Zhong et al. 1997b, 1999a, b; Prieto and Loske 1999; Loske et al. 2004b), reflector inserts to reduce tissue damage (Zhong and Zhou 2001), dual-phase reflectors (Bailey 1997b; Loske and Prieto 2001), dual-spark systems (Zhong et al. 1997b), piezoelectric tandem shock wave sources (Loske et al. 2002b, c, 2005; Arora et al. 2005; Fernández et al. 2005, 2009a, b), electromagnetic shock wave generators (Pierre et al. 2008), as well as combined electrohydraulic and piezoelectric tandem shock wave sources (Xi and Zhong 2000; Zhou et al. 2004b). Implementing some of the aforementioned technologies into clinical devices seems to be promising. For clinical uses in SWL, a relatively long time (about one second) would pass before the next tandem shock wave, i.e., the following pair of shock waves would be emitted. It is expected that, as occurs with single-pulse shock waves, reducing the rate of tandem shock waves would improve treatment efficiency.

Before modifying experimental shock wave sources and designing new SWL equipment, numerical models are helpful to study bubble dynamics and evaluate the potential fragmentation efficiency of a novel pressure profile. The maximum radius achieved by a single bubble after shock wave passage or the bubble radius at the second collapse (*inertial collapse*) (Fig. 4.8) have been used as an indirect measure of bubble collapse energy (Field 1991; Iloreta et al. 2007; de Icaza-Herrera et al. 2015). The larger a bubble expands, the smaller its final radius (after inertial collapse) is and the more violent a real bubble collapse would be. An example of this methodology was the design of the so-called *modified* tandem shock waves, i.e., a standard lithotripter shock wave followed by a pressure wave with relative large positive (and negative) pulse duration (Fig. 4.12). In a tandem shock wave profile consisting of two lithotripter shock waves, the positive phase of the second shock wave is shorter than the bubble collapse time. Because of this, the negative pulse of the second shock wave arrives during collapse, reducing its intensity. Much smaller bubble radii at second collapse were obtained using the modified pressure profile, because a positive pressure was present during the whole collapse. Furthermore, increasing $t_{\mathrm{FWHMp^+}}$ (Sect. 3.2) of the second pulse could enhance bubble collapse over a broad range of delays (Canseco et al. 2011).

The Gilmore–Akulichev equation was also used to show that both stress inside the stone and cavitation could be enhanced using a pressure pulse with relative long $t_{\mathrm{FWHMp^+}}$, which reaches the stone within hundreds of microseconds after two 20 μs-delayed initial shock waves (de Icaza-Herrera et al. 2015). Tham et al. (2007)

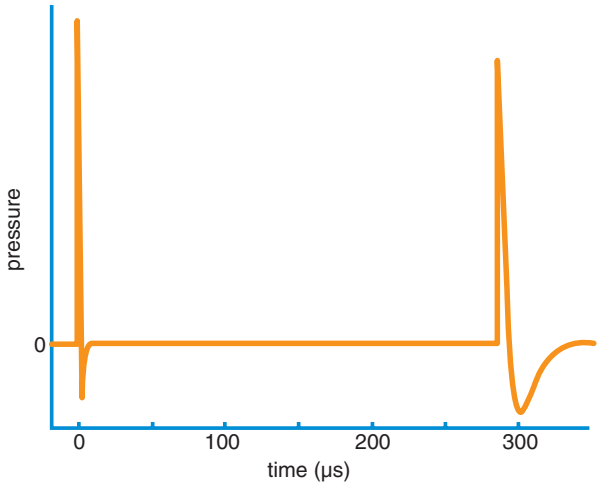


Fig. 4.12 Pressure profile of a modified tandem shock wave, consisting of a standard lithotripter pulse followed by a pressure wave with a relatively long positive and negative pulse duration

simulated the propagation of tandem shock waves to study the influence of very short delays on kidney stone fragmentation. Their results revealed that stress waves inside the stone interfere either constructively or destructively with each other depending on the delay between the shock waves. The main conclusion was that tandem shock waves with a delay as short as 20 μs could be used during the initial phase of a shock wave treatment to break up kidney stones into several large pieces. These short-delay tandem shock waves could be useful in cases where cavitation cannot contribute to pulverization; that is, if the stone is not surrounded by fluid, as may be the case of uroliths trapped in the ureter. Figure 4.13 shows the two shock waves proposed by Tham et al. (2007) to increase stress inside the stone, followed by the pressure pulse with extended $t_{\mathrm{FWHMp^+}}$ to enhance bubble collapse intensity. Using this pressure profile, numerical simulations predict that the second shock wave does not reverse bubble growth at the early stage of the expansion, so that theoretically both stone comminution mechanisms (stress and cavitation) could be increased simultaneously (Fig. 4.14). Implementing a pressure profile as the one shown in Fig. 4.13 into clinical devices could be feasible, especially with piezoelectric shock wave sources. In vitro and in vivo experiments will reveal if adding the 20 μs-delayed pulse significantly improves stone fragmentation.

Terms like tandem and *dual-pulse* shock waves have sometimes been used interchangeably; however, dual-pulse shock waves may be generated at too long delays to be useful as tandem pulses. As described in the final chapter of this book, tandem shock waves may be useful not only to improve SWL, but also to enhance the bactericidal effect of shock waves (Alvarez et al. 2008), and to increase the efficiency of genetic transformation (Loske et al. 2011, 2014), cell transfection, and cancer treatment (Lukes et al. 2014).

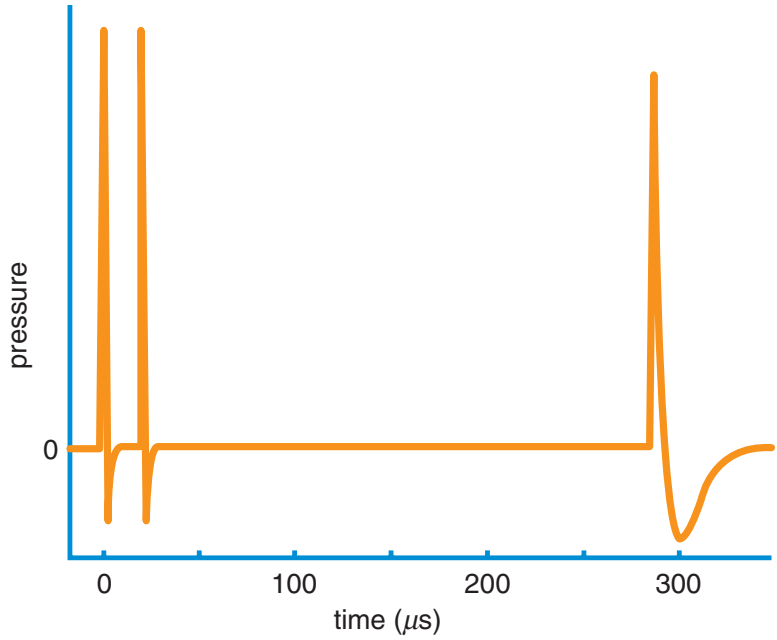


Fig. 4.13 Pressure profile of two 20 µs-delayed standard lithotripter pulses followed by a pressure wave with a relatively long positive and negative pulse duration

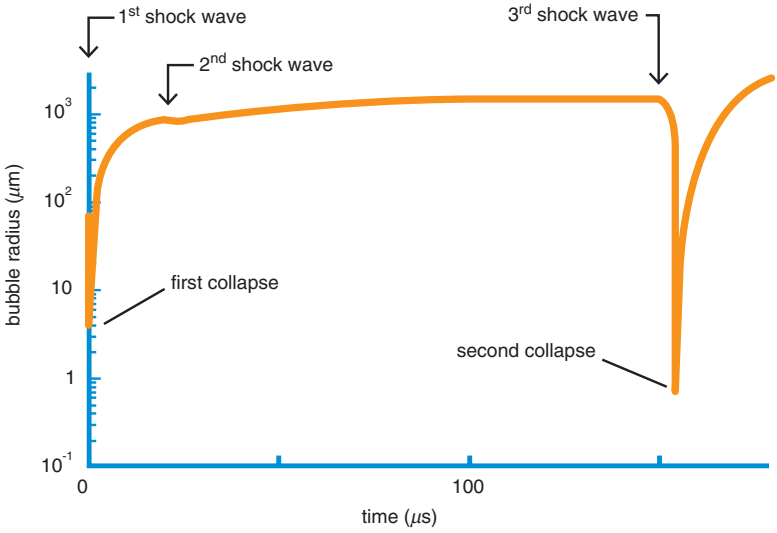


Fig. 4.14 Graph of a numerical simulation showing the variation of the radius of an air bubble in water (initial radius R_0=0.07 mm) exposed to the pressure profile shown in Fig. 4.13. The second collapse occurred approximately 155 µs after arrival of the first shock wave at t=0. (Courtesy of M. de Icaza-Herrera)

4.8 Circumferential Compression

Circumferential compression, also referred to as *circumferential squeezing*, contributes to stone fragmentation during SWL (Eisenmenger 2001; Eisenmenger et al. 2002; Eisenmenger and Kaatze 2007; Sapozhnikov et al. 2007). It occurs since the wave velocity in the fluid surrounding the stone is lower than the elastic wave velocity inside the stone. When passing from a fluid (urine) to a solid structure like a kidney stone, the shock wave increases its speed from approximately 1500 m/s to values between about 2000 and 6000 m/s. Because of this, the shock front inside the stone is always ahead of the front propagating outside the stone, and a circumferential pressure is exerted on the stone (Fig. 4.15). As a consequence, tensile stress inside the stone leads to failure and, as the treatment progresses, stone fragments undergo the same effect. Because the fracture strength of most stones is relatively low, shock waves with a peak-positive pressure of less than 30 MPa may be sufficient to fracture them. The initial publications on the contribution of circumferential compression to stone comminution during SWL stimulated some manufacturers to

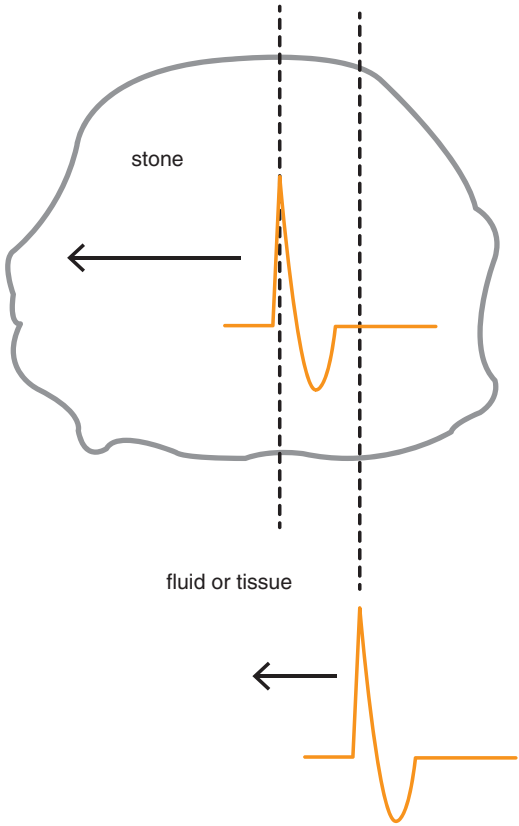


Fig. 4.15 Schematic of a shock wave traveling through a kidney stone from right to left, at a higher velocity than the shock front propagating in the same direction along the fluid or tissue surrounding the stone

design extracorporeal lithotripters with larger focal sizes and lower pressures (Eisenmenger et al. 2002).

Cleveland and Sapozhnikov (2005) developed a model that accounts for transmission, reflection, mode conversion, and diffraction of shock waves hitting a stone. Sapozhnikov et al. (2007) used the predictions of this model and performed thorough in vitro stone phantom fragmentation tests to prove that shear waves initiated at the corners of the stone and driven by squeezing waves along the calculus led to the greatest stress.

4.9 Other Fragmentation Mechanisms

Fatigue is a well-known phenomenon that occurs when materials are stressed repeatedly. It has been extensively studied in metals and could appear in urinary stones exposed to shock waves. After repetitive compression and tension, cracks can originate at micro-flaws inside the stone. Dynamic fatigue appears mainly because stones are not homogenous. Since the stress that a stone can resist decreases as the number of applied shock waves increases, it is possible to break a stone even if the maximum stress that the intact stone can withstand is higher than the compressive and tensile components of the lithotripter shock waves (Lokhandwalla and Sturtevant 2000).

Superfocusing and resonance are two phenomena that also could occur inside a urinary stone during SWL; however, their effects on stone fragmentation efficiency are supposed to be rather small. It has been suggested that depending on the composition and the shape of the stone, certain parts of it may concentrate shock waves to small regions of high stress. These regions called *caustics* may lead to stone fragmentation. Resonance occurs when a system vibrates in phase with an external oscillatory force. Since lithotripter shock waves have a broad frequency spectrum, some frequencies could coincide with the natural frequency of the urinary stone, enhancing vibrations inside it and contributing to the formation of cleavage planes.

4.10 Radiation Pressure

As mentioned above, mechanical waves carry energy and, as a consequence, exert forces on objects in their path. If a plane wave hits a wall normally to the wall, and if the wall is a perfect absorber, the radiation pressure exerted by the wave on the wall is proportional to the intensity of the wave. In the case of an ideal reflecting surface, the radiation pressure on the surface would be twice as large as for the absorber. In a real scenario, the wave is partially reflected and partially absorbed and the radiation pressure has a value in-between the aforementioned values. Furthermore, if the incoming wave is not plane, other phenomena have to be considered. In this case the resulting equations to calculate the radiation pressure are

more complex (Beissner 1987; Torr 1984; Sapozhnikov and Bailey 2013). Even if the radiation force of shock waves has not been associated with significant effects in clinical applications, as explained in Chap. 5, a device to reposition kidney stones using the radiation force of short bursts of focused ultrasound has been developed and tested (Shah et al. 2010b, 2012; Sorensen et al. 2013; Harper et al. 2014, 2016).

4.11 Sonoluminescence

Sonoluminescence is the process of producing electromagnetic radiation by the growth and collapse of a gas bubble in a fluid subjected to a pressure variation (Walton and Reynolds 1984). It can be distinguished between two types: single-bubble sonoluminescence (SBSL) and cavitation-field sonoluminescence (CFSL). SBSL refers to sonoluminescence from stable cavitation, a phenomenon mentioned above, i.e., light emission from a single bubble trapped in a liquid (Gaitan et al. 1992; Matula et al. 1997). CFSL is emitted by multi-bubble acoustic cavitation fields such as those generated by shock wave sources designed for some clinical applications (Matula et al. 1997). In this case, most bubbles disintegrate after shock wave passage. Sonoluminescence generated by a cavitation field is also referred to as multi-bubble sonoluminescence (MBSL).

Coleman and colleagues reported that sonoluminescence correlated with acoustic emissions from collapsing bubbles in the focal zone of an electrohydraulic lithotripter (Coleman et al. 1992, 1993). Even if this was an interesting finding, its influence on stone fragmentation during SWL is considered negligible. Nevertheless, sonoluminescence can provide important information on shock wave-induced cavitation (Matula et al. 1998; Wang et al. 1999b). Furthermore, the effects caused by sonoluminescence could be relevant in other biomedical uses of shock waves.

Because of the high collapse velocity of a bubble subjected to a shock wave in a fluid, the process is almost adiabatic (without heat transfer to the outside of the bubble). Bubble collapse stops due to the repulsive forces between the gas molecules inside the bubble. At this instant, the temperature inside the bubble is extremely high and the energy is large enough to break apart molecules, which emit an ultraviolet flash as they recombine. Matula and colleagues (2002a) studied the sonoluminescence and sonochemistry resulting during both forced bubble collapse and inertial collapse. According to their results, bubbles obtain much higher temperatures during the forced compression than during the following inertial collapse. A thorough theoretical study of bubble dynamics and sonoluminescence was reported by Kamath et al. (1993). The relationship between sonoluminescence and cell membrane permeabilization and viability was studied by Cochran and Prausnitz (2001). Specialized information on sonoluminescence can be found in a book on bubble dynamics published by Leighton in 1994, a review by Ohl et al. (1999), and the excellent guide published by Crum (2015).

4.12 Mechanisms of Tissue Damage During SWL

Tissue damage is a complex phenomenon that has not yet been fully understood. During SWL, living tissue is exposed to most of the mechanisms mentioned above. Their contribution to tissue injury depends on the shock wave source, the energy, the pressure profile, the coupling device, the path followed by the shock waves, the age, sex, body mass index (BMI) and health of the patient, and the region of the body exposed to the pressure field. Unfortunately, the physical parameters defined in Chap. 3 do not allow precise statements to be made about shock wave-induced biological effects.

The effects of shock wave interactions with tissue and tissue-mimicking structures have been studied by many authors (Delius et al. 1987, 1988a, c, 1990a; Woodruff and Kandel 1987; Abrahams et al. 1988; Fischer et al. 1988; Jaeger et al. 1988; Neisius et al. 1989a, b; Recker et al. 1989; Brümmer et al. 1990; Mayer et al. 1990; Clayman et al. 1991; El-Damanhoury et al. 1991b; Evan et al. 1991, 1998a, b, 2003; Kaji et al. 1991; Ryan et al. 1991; Rassweiler et al. 1993; van Leeuwen et al. 1993; Roessler et al. 1993; Delius 1994; Raeman et al. 1994; Anderson et al. 1995; Sarica et al. 1996; Howard and Sturtevant 1997; Willis et al. 1999; Miller and Song 2002; Chen et al. 2010, 2012; Connors et al. 2012). During SWL, shock wave energy has been correlated with stone disintegration, while EFD is considered by some authors as one of the most important factors for tissue trauma. This was confirmed by in vitro studies with isolated perfused kidneys reported by Bergsdorf et al. (2005a).

In vitro studies revealed that shock waves may cause permeabilization of cell membranes (Sect. 7.4), cell fragmentation, swollen mitochondria, alterations in the vimentin structure, cytoplasmic cisternae, and nuclear changes (Russo et al. 1986; Randazzo et al. 1988; Bräuner et al. 1989; Kohri et al. 1990; Clayman et al. 1991; Lifshitz et al. 1997). Cavitation and shear stress are supposed to be the main mechanisms responsible for shock wave-induced tissue damage (Lokhandwalla et al. 2001). Freund et al. (2007) suggested that shear forces produce the first rupture in the microvasculature. Common traumas are hemorrhaging and edema within or around the kidney. According to the study by Evan and colleagues (1998b) SWL induces renal injury that extends from the papilla to the outer cortex, modifying renal function in most patients. Munver et al. (2002) reported that shock waves may produce oxidative stress in the renal cortex. Most shock wave sessions produce injury to the nephrons and to small-to-medium-sized blood vessels. Other authors (Rubin et al. 1987) detected subcapsular hematoma, subcapsular fluid collection, intrarenal hematoma, and perinephric soft tissue stranding and fascial thickening of the renal fossae on CT scans of SWL-treated patients. According to the other reports, in 24–85 % of all SWL patients, magnetic resonance imaging (MRI) and CT revealed intrarenal and subcapsular hematoma (Kaude et al. 1985; Baumgartner et al. 1987; Rubin et al. 1987; Littleton et al. 1989; Evan et al. 1991). The presence of hematomas is known to increase with the age of the patient (Dhar et al. 2004). Serious complications such as gastrointestinal injury have only been reported in few cases (Maker and Layke 2004).

Acoustic waves cause rapid compressions and expansions as they propagate through living tissue. This may produce heating, cavitation, compression, shear, and structural changes. Heating occurs because of energy absorption within the tissue, i.e., acoustic energy is transformed into heat. It depends on the intensity of the acoustic radiation, its waveform, and the type of tissue. Fortunately, thermal injury to soft tissue can be ignored at the energy levels used in SWL and ESWT (Filipczynsky and Wojcik 1991; Ueberle 2011).

If a shock front passes through soft tissue, material flows could be induced behind it (Kodama and Tomita 2000). Turbulence or acoustic streaming may occur at liquid/solid or at gas/solid interfaces. As mentioned before, if a shock wave propagates from a medium with higher acoustic impedance towards a medium with lower impedance, the sign of the reflected pressure becomes negative, i.e., the positive pressure pulse is reflected as a negative pulse. An example could be shock wave passage through air-filled cavities inside the lungs. Since most of the energy is reflected at the tissue–air interface, strong forces appear, and the tissue tears. Care should be taken with all gas-filled cavities inside the body (Dalecki et al. 1997; Raeman et al. 1994). Furthermore, if shock wave coupling is not done properly, i.e., if air bubbles are left between the membrane and the patient, skin injury at the shock wave-entrance site may occur. It normally disappears spontaneously within a few days.

Most of the in vivo studies on shock wave-mediated tissue injury have been made with the Dornier *HM3* lithotripter. When analyzing these results it is important to keep in mind that tissue damage produced by other extracorporeal lithotripters may be significantly different. As already mentioned, the peak compression at the focus of a shock wave source as used for clinical applications can be up to 150 MPa. Even though this pressure acts only for a very short time, it is surprising that soft tissue can withstand such high pressure variations at all. Nevertheless, shock waves with enough energy to pulverize urinary stones can produce tissue damage. The risk of side effects increases whenever the shock wave energy is raised to enhance stone fragmentation. Renal injury and long-term adverse effects depend on the dose (EFD and number of shock waves) applied (McAteer et al. 2009).

The first studies on shock wave-induced tissue trauma showed that exposure of the abdomen of rats as well as of eventrated isolated liver, kidneys, and intestines did not cause pathologic changes; however, when the rat thorax was exposed to shock waves, severe lung damage occurred (Chaussy 1986; Chaussy et al. 1976). Chaussy and colleagues (1976) observed that shock waves focused on kidneys or on implanted stones in the renal pelvis of dogs only resulted in slight and transient tissue trauma of the kidney tissue. In vivo shock wave exposure of the liver and the gallbladder of dogs caused minimal ecchymoses (extravasation of blood). Pressure-dependent pulmonary tissue damage was also observed in dogs, after exposing their gallbladder to shock waves (Delius et al. 1987). Using an electrohydraulic shock wave source, the same group reported gross lung hemorrhages in dogs at up to 150 mm from the focal spot, along the shock wave path. In contrast to these observations, biliary SWL with electrohydraulic lithotripters in humans did not cause lung hemorrhages (Sackmann et al. 1988; Sauerbruch and Stern 1989).

Even if at the beginnings of SWL it was believed that shock waves do not cause renal trauma and that no adverse long-term effects are produced after treatment, more extensive studies suggested that certain degree of tissue damage, including mild hematuria, subcapsular or perinephric hematomas, renal vasoconstriction and, in rare cases, excessive bleeding can develop (Evan et al. 1998b; Connors et al. 2000; Evan and Willis 2007; McAteer and Evan 2008). Shock wave-induced tissue injury may contribute to tissue hypoxia and promote oxidative stress. An inflammatory response at the sites of endothelial injury, and a reduction in the glomerular filtration rate (GFR) and renal plasma flow (RPF), is to be expected after almost every SWL. Inflammatory cells have been detected in the renal parenchyma within 30 min after shock wave treatment (Banner et al. 1991; Evan et al. 1998b; Evan and McAteer 1996b). Sarica et al. (1996) reported that oxidative stress mediated by ischemia-reperfusion (tissue damage caused when blood returns to tissue after a period of ischemia) could be responsible for renal injury subsequent to SWL. Clark et al. (2009) reported that the initial SWL-injury is vascular. Subsequently, the blood from ruptured vessels pools in the renal parenchyma. This may produce ischemia and oxidative stress.

The risk of cavitation-induced tissue damage increases at high shock wave rates. A common side effect of SWL is bloody urine due to tissue damage in the kidney. Elderly patients, children, and patients with hypertension are more vulnerable to suffer complications because of shock wave-induced renal trauma (Janetschek et al. 1997; Lifshitz et al. 1998; Willis et al. 1999). Transient macrohematuria, interstitial edema, and temporary loss of kidney function have been reported after SWL by several authors (Woodruff and Kandel 1987; Fischer et al. 1988; Evan and Willis 2007). It is believed that hematuria is a result of cortical and medullary hemorrhage, tubular dilation, and glomerular bleeding. If SWL is properly performed, the organs adjacent to the kidney are not affected (Abrahams et al. 1988; Hill et al. 1990).

The tensile strength for human renal parenchyma is relatively low (Kodama and Tomita 2000). Because of this, tissue rupture can occur during SWL. According to the publications by Köhrmann et al. (1995) and Piper et al. (2001), extracorporeal lithotripters with small focal zones and high peak pressures resulted in higher hematoma rates than shock wave sources that generate large focal volumes and low treatment pressure. However, more recent studies including a large number of patients treated with a small-sized focal zone lithotripter (*Modulith SLX-F2*, Storz Medical AG, Tägerwilen, Switzerland) revealed a very low (0.34 %) symptomatic perinephric hematoma incidence (Razvi et al. 2012). Significant risk factors included intraoperative hypertension and anticoagulant/antiplatelet medications.

Plenty information on shock wave injury to the kidney comes from experiments with pigs and dogs (Banner et al. 1991; El-Damanhoury et al. 1991b; Willis et al. 1996; Blomgren et al. 1997; Connors et al. 2000, 2012; Sapozhnikov et al. 2001; Shao et al. 2003; Handa et al. 2007, 2009b; Evan et al. 2008). A correlation between peak pressure and renal trauma was reported by El-Damanhoury et al. (1991b) in pigs and by Rassweiler et al. (1993) in dogs. Studies with a pig model found that the renal papilla is particularly susceptible to shock wave damage. To reduce the number of in vivo experiments, some authors developed well-standardized ex vivo

kidney models to evaluate tissue damage due to SWL (Köhrmann et al. 1994; Bergsdorf et al. 2005a); however, even if ex vivo experiments reveal important aspects of tissue damage, the results differ from the clinical scenario. Using ex vivo models it was found that the EFD influences renal vascular lesion and that renal injury is not directly influenced by p^+ and by the focal size (Häcker and Wess 2010). Other groups performed studies with perfused kidneys and reported different dose-dependent morphologic findings, such as damage to venules in the medulla, and rupture of cortical arterioles (Rassweiler et al. 1993). Gels and vessel phantoms have also been used to simulate tissue and blood vessels (Kodama and Tomita 2000; Brujan et al. 2001a, b; Zhong et al. 2001).

Matula et al. (2002a) reported that oxidative tissue damage can occur both due to free radicals produced by shock wave-induced bubble collapses and from reperfusion of injured areas. Delvecchio et al. (2003) exposed the right lower pole of pigs to shock waves and analyzed markers of oxidative stress within the renal cortex during treatment. Their goal was to analyze if biochemical evidence of cellular injury could be found in ipsilateral locations remote from the shock wave-application site or in the contralateral kidney. The highest level of oxidative stress was detected at the focus of the lithotripter. An increase in free radical activity at sites remote from the treated regions was also observed, suggesting detrimental global effects. According to the authors, their findings could be related to vasoconstriction throughout the treated kidney with resultant ischemia-reperfusion injury.

Connors et al. (2012) used a pig model to evaluate the in vivo tissue injury produced by a *Modulith SLX-T* extracorporeal lithotripter (Storz Medical AG). Healthy kidneys were exposed to 2000 or 4000 shock waves at power level 9 and a shock wave rate of 2 Hz, or 2000 shock waves at a rate of 1 Hz. GFR and RPF were evaluated before and 1 h after shock wave treatment. Histological analysis and morphometric quantitation of the hemorrhage in the renal parenchyma were also performed. The results were compared with data from a similar study using an unmodified Dornier *HM3* (Connors et al. 2009b). Even if the *Modulith* produced a more focused and intense lesion running from the cortex to the medulla, measures of the lesion size based on macroscopic determination of hemorrhage in the parenchyma were not significantly different from kidneys treated with 2000 shock waves at 2 Hz on the *HM3*. The authors concluded that although the lesions created by the *Modulith* lithotripter were more pronounced, this does not mean that such an injury is more consequential. Furthermore, it is important to mention that the *Modulith* was used at a power level that generated much higher p^+ values than the *HM3* at the voltage-setting used by Connors and his group. It is very likely that the morphological damage produced by the Storz device in this study would have been less at lower power settings. Moreover, in a real SWL the stone and not healthy tissue is located at the focal volume of the lithotripter. This is especially relevant for lithotripters with small focal volumes. Another fact that hinders direct comparison is that the *Modulith* generates very consistent pulses, while the *HM3* produces large pressure fluctuations and movement of the focal zone from shot to shot. Doubling the number of shock waves with the *Modulith* did not significantly increase the size of the lesion. The renal function reduced after all treatments and was similar for both shock wave

sources. An interesting finding was that slowing the shock wave rate of the *Modulith* from 2 to 1 Hz did not reduce the size of the lesion, as occurred with the *HM3*.

It is known that ultrasonically excited microbubbles may induce vessel rupture (Ye and Bull 2006; Miao et al. 2008). To produce certain bioeffects it is convenient to control cavitation. Shock wave-induced bubble expansion as well as invagination of vessels during bubble collapse may cause vascular damage. A more detailed knowledge on how cavitation bubbles develop within tissue would be useful for most biomedical shock wave applications. As mentioned before, acoustic cavitation is one of the most important stone comminution mechanisms, but it may also contribute to cell and tissue trauma during SWL (Delius et al. 1990a, b, c, 1998; Coleman and Saunders 1993; Huber et al. 1994; Coleman et al. 1996; Carstensen et al. 2000; Cleveland et al. 2000b; Sapozhnikov et al. 2001; Zhong et al. 2001; Evan et al. 2002; Zhu et al. 2002). The negative phase of a shock wave converging towards the focal spot of a shock wave source can exceed the threshold for cavitation in urine or blood, inducing bubble growth and collapse. Fortunately most mammalian soft tissue has only few cavitation nuclei. Furthermore, cavitation inside living tissue is reduced because the rise time of the shock waves increases as they propagate through tissue. Karlsen et al. (1991) observed that hemorrhage is associated with trauma in arteries, capillaries, and veins. Damage to vessel walls has been detected after bubble collapse in mesentery vessels (Chen et al. 2011). An experimental study published by Zhong and colleagues (2001) demonstrated that small blood vessels are at higher risk for mechanical rupture than large blood vessels. Cavitation seems to be responsible of initiating renal trauma by the rupture of blood vessels having a diameter of about 8–30 μm (Weber et al. 1992; Cleveland and McAteer 2012). The bubble diameters involved in tissue injury are estimated to be between 1 and 100 μm (Coralic 2014); however, it is believed that the blood vascular system does contain only few cavitation nuclei, because bubble growth and collapse does not start from the beginning of an SWL session (Carstensen et al. 2000). According to Coralic (2014), at the beginning of an SWL treatment, the density of cavitation nuclei (not larger than 1 μm in diameter) is about 2.7 nuclei per liter of blood; however, as the number of shock waves rises, bubble splitting increases the number of cavitation nuclei. Evan and colleagues (1998b) reported that it takes approximately 1000 shock waves, before extensive cavitation signals are detected. Blood pooling may be a precursor to cavitation in blood vessels (Shao et al. 2003). After shock wave passage through urine, bubbles are formed readily; however, as mentioned before, in tissue cavitation was observed only after hundreds of shock waves (Bailey et al. 2005). As long as the cavities inside the tissue are small, either no liquid microjets are formed, or they do not cause observable damage.

Williams and coworkers (1999) exposed red blood cells in vitro to shock waves from an electrohydraulic lithotripter. The experiments were performed under hydrostatic pressure (up to 120 atm) to inhibit bubble formation. Significant cell lysis was detected, demonstrating that injury occurred due to mechanisms other than cavitation. Because cavitation has been observed much less in vivo than in vitro, the non-cavitational mechanisms observed in this study could be a significant part of the cell disruption that has been reported in vivo. The authors suggested that shock wave-

induced cell lysis may be due to shear, i.e., differential tissue motion. Another group also studied injury to isolated red blood cells due to focused shock waves in a cavitation-free environment. Their results validate the hypothesis of shear-induced cell lysis (Lokhandwalla and Sturtevant 2001; Lokhandwalla et al. 2001). Regardless of this, several authors have studied the feasibility of controlling cavitation to reduce tissue damage (Arora et al. 2005). Reducing the tensile component of a lithotripter shock wave and, as a consequence, acoustic cavitation has been proposed to reduce vascular injury (Zhu and Zhong 1999). A method to achieve this is the use of an acoustic diode. Zhu et al. 2004 demonstrated that the number of shocks needed to cause rupture of a small blood vessel phantom increased significantly when using an acoustic diode. The device consisted of two acoustically transparent membranes fastened to a metallic ring to form a cavity. A partial vacuum was applied to the cavity so that both membranes were in contact. The positive pressure pulse of the shock wave passed through both membranes almost without being reflected, because there was no gap between the membranes; however, the negative phase of the shock wave separated the membranes, creating a high acoustic impedance difference, significantly reducing the transmission of the tensile wave. Before using such a diode in SWL it must be calibrated so that the reduction in the trailing negative phase of the shock waves does not decrease the fragmentation efficiency.

The use of ultrasound contrast agents during shock wave treatment could significantly increase vascular injury. The size of microbubbles (shells of denatured albumen) in commercial ultrasound contrast agents is about 1–10 μm; however, at pressures generated by clinical shock wave focusing devices, bubble formation can be induced in blood vessels having cavitation nuclei as small as 20 nm in diameter (Zhong et al. 1998a). Dalecki and colleagues (1997) studied the influence of ultrasonic contrast agents on the hemorrhage produced by low-amplitude pressure pulses in mice and reported that the cavitation nuclei of the contrast agent significantly increased tissue damage. Other studies revealed that using phase-reversed waveforms or tandem-delayed shock waves may reduce tissue damage (Zhong and Zhou 2001; Evan et al. 2002). Matlaga et al. (2008) performed extensive in vivo experiments with pigs to estimate the spatial distribution of hemorrhagic lesions caused by a Dornier *HM3* lithotripter when the vasculature was seeded with cavitation nuclei (polystyrene microspheres). Their results revealed that the wide distribution of damage suggests that the *HM3* delivers negative pressures that exceed the cavitation threshold far off the beam axis.

To study shock wave–bubble interactions in tissue using numerical analysis is complex. Kobayashi et al. (2011) simulated non-spherical bubble collapses near several soft tissue boundaries and reported that the reflection wave of an incident shock wave at a tissue boundary is the primary cause for the acceleration or deceleration of bubble collapse. Freund et al. (2009) investigated the interaction of microjets with viscous liquid (that served as a model for tissue) using numerical simulations. According to their results, viscosities comparable to that of soft tissue significantly suppress penetration of cavitation-induced microjets; however, the generated shear stresses could damage cells. Coralic (2014) developed a numerical scheme to simulate the three-dimensional collapse of a bubble in both the free-field and inside a vessel phantom and analyzed its role in vascular injury. The author concluded that

bubbles smaller than 1 μm in diameter are unlikely to rupture blood vessels; however, as an SWL treatment progresses bubbles capable of vascular rupture may appear.

Shock wave-induced shear stress might initiate injury in kidney tissue; however, it seems that a single shock wave does not generate sufficient shear to rupture soft tissue. Freund et al. (2007) studied the effect of shear on kidney tissue implementing a simulation model, wherein the tubules and vessels in the inner medulla were represented as elastic shells surrounded by viscous fluid. According to their analysis, tissue-damaging stress can build up in the kidney tissue if the shock wave delivery rate is higher than the relaxation time of the tissue.

To evaluate whether SWL could cause injury to the endocrine cells of the pancreas, leading to the development of diabetes mellitus (DM), Wendt-Nordahl et al. (2007) analyzed the serum levels of amylase, lipase, insulin, glucose, c-peptide, and glucagon of patients treated with shock waves for proximal ureteric or kidney stones. The control group was formed by patients treated with shock waves for distal ureteric stones. Their results revealed no effect on the serum levels of variables indicating exocrine or endocrine pancreatic tissue damage caused by SWL. According to this study it seems unlikely that SWL leads to pancreatic trauma with consecutive development of DM. The results of experiments on pigs predisposed to DM were similar (Handa et al. 2014, 2015a, b).

To test if cavitation at the focus of an extracorporeal lithotripter can generate biologically damaging ultraviolet radiation and X-rays, Vona et al. (1995) exposed gassy water to ten shock waves generated with a piezoelectric shock wave source (p^+ approximately 43 MPa) and measured the resultant sonoluminescence with a photomultiplier tube. Additionally, a scintillation cocktail, that converts high energy photons to visible light, was exposed to varying numbers of shock waves. The luminescence intensity was measured and compared to background and distilled water luminescence readings. The authors concluded that their results show support for the hypothesized emission of ultraviolet radiation (approximately 250 nm) and marginal support for the production of higher energy photons.

Some methods described in Chap. 5, such as adjusting a slow shock wave delivery rate, slowly increasing the shock wave energy during SWL, and the use of prophylactic shock waves at the beginning of the treatment, followed by a brief pause, are options to minimize renal injury during SWL.

4.13 Interaction of Shock Waves with Tissue During ESWT

As mentioned before, if shock waves reach a boundary, such as a muscle-bone or a tissue–air interface, wave reflections occur and desirable or non-desirable phenomena may be expected. The type and severity of tissue damage as well as the desired effects that focused shock waves cause may be different from those created by unfocused shock waves or by radial pressure waves. For novel clinical uses of shock waves and radial pressure waves, extensive studies are mandatory to

determine the therapeutic range to improve treatment efficiency while minimizing tissue trauma and secondary effects.

As occurs during SWL sessions, the interaction of pressure pulses with living tissue depends on several factors, some of which can be controlled and some cannot. The total energy applied to the tissue during ESWT, the frequency spectrum, the applied pressure profile, as well as the pulse repetition frequency may influence treatment outcomes (Dreisilker 2010c). Most studies indicate that the effects of shock waves on tissue depend mainly on the EFD and the number of shock waves; however, so far there is no consensus on which shock wave parameters are responsible for which response at the cellular level. The path of the pressure waves through the patient's body, coupling of the energy into the patient, the therapeutic zone of the pressure wave source, and an adequate targeting are also crucial.

Effects of ESWT are related to biological reactions to mechanical stimulations (Suhr and Bloch 2012; Bloch and Suhr 2014; d'Agostino et al. 2015). Both direct and indirect pressure wave related phenomena generate biological responses. Biological tissue has the capability to sense different types of stress and transmit the information into the cellular system. The process, referred to as *mechanotransduction* has been observed in tendons, skeletal muscle, cartilage, endothelium, and connective tissue. Mechanotransduction involves the translation of physical stimuli into biochemical signals (Jaalouk and Lammerding 2009). A mechanoreceptor allows bone cells to react to mechanical stimulation, converting biophysical stimuli into biochemical signals that can modify the expression of genes and cellular adaptation (Moralli et al. 2000). It is known that compression and tension forces acting on shock wave-exposed tissue increase microscopic circulation enhancing the metabolism at this region, promoting healing processes by changing the membrane permeability and causing the development of stress fibers. Shock waves stimulate osteoblasts, i.e., the cells responsible for bone healing and production of new bone, as well as fibroblasts, the cells in charge of healing processes of connective tissues.

Tissue regeneration, neovascularization, and hyperstimulation analgesia are believed to occur as a consequence of a cascade of molecular events. Some reported shock wave-induced biochemical effects are hyperpolarization and Ras (proteins involved in transmitting signals within cells) activation (Wang et al. 2001d, 2004a), induction of intercellular gaps (Seidl et al. 1994), and non-enzymatic nitric oxide synthesis (Gotte et al. 2002). Many reports are focused on shock wave effects, such as nerve and axonal regeneration (Hausner et al. 2012), reduction of oxidative stress and inflammation (Clark et al. 2011), enhancement of endothelial capillary connections (Sansone et al. 2012), collagen matrix changes (Bosch et al. 2009), and recruitment and differentiation of stem cells or progenitor cells (Sun et al. 2013). In cases of tendinopathy that can be associated with calcium deposition, shock waves may promote resorption of calcium, thereby decreasing pain and improving function.

Shock wave-induced cavitation bubbles can break calcific deposits and stimulate axons, inducing analgesic effects. Ex vivo experiments done by Schelling and colleagues (1994) revealed that shock waves excite nerves. Interestingly, this was only observed as long as tiny gas bubbles were present in the organ bath where the nerves were immersed, demonstrating that the phenomenon was induced by acous-

tic cavitation. As mentioned in Sect. 3.5, in the case of radial pressure waves, the EFD decreases rapidly as the distance from the source increases. Because of this, tissue damage due to cavitation during radial pressure wave therapy is expected to be less; however, this depends on the number of applied pulses, the energy and the device used. Trying to resemble the effect of radial pressure waves on human embryos, Kiessling et al. (2015) exposed chicken embryos *in ovo* to different doses of radial pressure waves. Their results revealed a dose-dependent increase in the number of embryos that died after treatment. Severe congenital defects were observed among the surviving embryos.

Väterlein et al. (2000) used macroscopic, radiologic, and histologic examination to demonstrate that an ESWT of 2000 shock waves (EFD = 1.2 mJ/mm^2) does not cause significant damage to the joint cartilage of immature rabbits. Other authors reported that ESWT may damage the endothelial tissue, increasing vessel wall permeability and, as a consequence, enhance diffusion of cytokines, which promote healing (Ogden et al. 2001a; Wang et al. 2002a, 2003b; Speed 2004; Wang 2012). Evidence that shock waves trigger mitogenic activities that remodel fibrosis tissue into new cartilage and bone also were important findings (Chen et al. 2004).

More recent in vitro experiments revealed that a dose-dependent effect of shock waves generates an increase in the gene expression of collagen (the main protein contained in the extracellular space) types I and III and the transforming growth factor TGF-β1, followed by the production of nitric oxide (NO) and collagen synthesis (Chao et al. 2008; Vetrano et al. 2011). Shock waves are also known to stimulate osteogenesis and chondrogenesis (the process by which cartilage is formed) in calluses. Yu et al. (2010) reported that ESWT promotes the adhesion and migration of rat osteoblasts.

Shock wave therapies are believed to up-regulate proteins like the vascular endothelial growth factor (VEGF) (Meirer et al. 2007), the bone morphogenic protein (BMP), the osteogenic protein (OP) (Wang 2012), and nitride oxide syntheses (Ito et al. 2009; Wang 2012). Increased levels of the placental growth factor (PGF) have also been detected after shock wave application (Meirer et al. 2007; Aicher et al. 2006). The PGF amplifies the angiogenic activity of the VEGF.

Bones possess mechanisms that sense external mechanical forces to manage bone formation. The forces are detected and transduced into chemical responses by cells called osteocytes. These cells release molecules which induce the activity of osteoblasts or osteoclasts (cells in charge of bone resorption during repair of bones) to alter the bones (Klein-Nulend et al. 2013). Shear stress can also influence the mechanoreceptors in cells by turning on mechanosensitive ion channels, heterotrimeric G proteins, protein kinases, and other signaling molecules. As a consequence, signaling cascades are triggered that lead to force-dependent changes in gene expressions (Wang et al. 2009d). Huang et al. (2013) reviewed how mechanical forces modulate integrin-mediated processes and other mechanosensors, such as gap junctions, hemichannels, cell targeting, and molecule targeting in various therapies, including ESWT. More information on the biological effects shock waves and radial pressure waves on tissue, from mechanical stimulation to healing, can be found in a review published by d'Agostino et al. (2015).

The effect of shock waves on bone and bone marrow has been studied in vitro and in vivo for several years (Graff et al. 1988a, 1989; van Arsdalen et al. 1991; Forriol et al. 1994; Delius et al. 1995a; Ikeda et al. 1999; Kusnierczak et al. 2000; Moralli et al. 2000; Wang et al. 2001d, 2002a, 2003a, 2008a; Chen et al. 2004; McClure et al. 2004b; Sathishkumar et al. 2008; Tischer et al. 2008; Suhr et al. 2013; Kertzman et al. 2015). Bones are fairly resistant to shock waves because of their crystalline composition and high percentage of collagen matrix. Since their tensile and compression strength do not differ much from each other, they cannot be considered brittle. Nevertheless, the acoustic impedance of trabecular bone (cancellous bone) is much higher than that of soft tissue (Robinson and Kossoff 1978). As a consequence, shock wave reflection generates tensile forces that might induce microfractures. Acoustic cavitation is also believed to cause trabecular microfractures and interstitial gaps. Shock waves have shown to produce subperiosteal hemorrhages at rabbit femora, and multiple trabecular fractures in the marrow cavity. New bone formation leading to considerable cortical thickening has been observed after shock wave treatment (Delius et al. 1995a).

Because the acoustic impedance of bone is higher than the impedance of bone cement and since there is no chemical bonding between bone and cement, shock waves can loosen the cement during revision arthroplasty. Preoperative shock wave application has been proposed (Weinstein et al. 1986); however, shock waves may liberate bone marrow particles, which could cause fat embolism (Braun et al. 1992).

The acoustic impedance of cortical bone is about five times higher than that of tissue. This has important consequences on the effects caused by shock waves on cortical bone. Shock waves may produce dose-dependent hemorrhage at the periosteum (membrane that covers all bones) and in the bone marrow as well as localized cell death, leading to revascularization. As a natural consequence, shock wave action stimulates new bone and tissue formation at the site of consolidation; however, a minimum acoustic energy is required to start the healing process. As will be described in Chap. 6, after the pioneering work by Valchanou and Michailov (1991) reporting bony unions in 70 of 82 patients with delayed or chronic non-union of fractures at various locations, and the article by Schleberger and Senge, demonstrating fracture healing in three of four pseudoarthroses treated with shock waves, several other studies were published on this topic (Schleberger and Senge 1992).

It is well known that physical stimuli activate endogenous pain control systems. Shock waves may reduce the transmission of pain signals from the sensory nerves (Huang et al. 2000; Ohtori et al. 2001; Takahashi et al. 2003). So far the detailed mechanisms involved in shock wave-mediated pain relief are not understood. New blood vessel formation (neovascularization) seems to be involved in the process (Furia 2005). The influence on the metabolism of substance P (an important transmitter of pain information into the central nervous system) may contribute to the analgesic effect of ESWT (Maier et al. 2002). Andersson et al. (2011) reported that substance P accelerates hypercellularity and angiogenesis in tendon tissue and enhances paratendinitis (inflammation of the sheath surrounding the tendon) in response to Achilles tendon overuse in a tendinopathy rabbit model. Other authors found that shock waves (EFD = 0.9 mJ/mm^2) applied to the distal femur of rabbits

in vivo resulted in an increased basal secretion of substance P after 24 h and a decreased secretion of substance P, attributable to degeneration of parts of the nerve endings, 6 weeks after shock wave treatment (Maier et al. 2003).

ESWT for muscle treatment is an alternative to manual trigger point therapy. The main goal is to reduce pain and muscle tone; however, the detailed mechanisms involved still need to be clarified. It is believed that some important shock wave-induced mechanisms in muscle treatment are improvement of blood circulation, dilution of vasoneuroactive substances, release of substance P, release and synthesis of nitric oxide, degeneration of C-fibers (a type of nerve fiber that carries sensory information), biological mechanotransduction, and destruction of damaged muscle fibers. The therapy is most effective when tendinopathies are treated together with the associated muscles, instead of purely locally (Gleitz 2011).

The treatment of tendinopathies is the most common ESWT therapy (see Chap. 6). So far, there is no consensus on whether ESWT activates the cells of a tendon directly, or if shock waves control the pathogenetic change of the extracellular matrix (ECM) homeostasis that takes place in tendinopathies. A reversible inflammatory reaction in tendon cells as well as a neovascular proliferation at the bone-tendon junction (BTJ) associated with the release of proangiogenic regulatory factors and proliferating cell antigen has been observed after experimental in vivo ESWT with rabbits (Rompe et al. 1998b; Wang 2003).

Antonic and Stojadinovic (2012) reported that not only increased tissue perfusion and oxygenation occurs after shock wave treatment to soft tissue, but also tissue vasculature permeability is influenced during ESWT. The authors published an overview of shock wave effects on components of the inflammatory response cascade, and the vascular and cellular response to shock wave therapy.

Shock waves at low EFD (0.03 mJ/mm^2) have been successfully used for anti-inflammatory therapy. A molecular mechanism that has been proposed to trigger the anti-inflammatory action of shock waves as used in the treatment of tendon and muscle tissues is the rise of NO production in cells, which is a vasodilatator that plays a critical role in inflammation (Mariotto et al. 2005, 2009). Increased NO levels and the following suppression of NF-kappaB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation could account for the beneficial effect of shock waves on tissue inflammation. NF-kappaB is a protein complex involved in cellular responses to external stimuli. It is found in animal cells and controls transcription of DNA and cell survival.

As already mentioned, shock waves are known to promote neovascularization, improving blood supply and tissue repair mechanisms (Wang et al. 2002a, 2003a). Aicher et al. (2006) found that shock waves improve recruitment of circulating endothelial progenitor cells, which is beneficial for patients with chronic ischemic disease (reduced blood supply). The mechanisms by which ESWT provides a therapeutic effect in wounds remain unclear. Several authors reported that shock wave-mediated wound healing in skin occurs through suppression of pro-inflammatory pathways and infiltration of macrophages and neutrophils (Davis et al. 2009; Kuo et al. 2009; Zins et al. 2010; Contaldo et al. 2012). According to an in vitro study by Sukubo et al. (2015), macrophage exposure to shock waves dampens the induction

of the pro-inflammatory profile characterizing M1 macrophages and promotes the acquisition of an anti-inflammatory profile synergizing with macrophage alternative activation.

In patients suffering from chronic pelvic pain syndrome (CPPS), ESWT is supposed to reduce pain by interruption of nerve impulses, hyperstimulation of nociceptors, revascularization processes, and reductions in spasticity (Marszalek et al. 2009; Zimmermann et al. 2009). A hypothesis is that extracellular disruption is produced as shock waves travel through the tissue, damaging local nerve endings (Ogden et al. 2001b).

Chapter 5
Shock Wave Lithotripsy

5.1 Introduction

Shock wave lithotripsy (SWL), also referred to as *extracorporeal shock wave lithotripsy* (*litho* = stone, *tripsy* = "to crush"), is the use of shock waves to comminute urinary stones without the use of invasive techniques. It still is the only available noninvasive therapy to remove urinary stones (Tiselius 2013a). Other common methods are ureteroscopy (URS), which is a procedure to remove ureteral stones using pneumatic, ultrasonic, or laser lithotripters, as well as stone basket retrievers by introducing an endoscope through the urethra and into the ureter, percutaneous nephrolithotomy (PNL), a procedure to remove especially hard and large stones from the kidney (using pneumatic, ultrasonic, or laser lithotripters) through a small caliber nephrostomy tract surgically created under radiographic or ultrasound guidance, and retrograde intrarenal surgery (RIRS), a technique to do surgery inside the kidney using a laser lithotripter by passing a flexible endoscope through the bladder and the ureter into the kidney. SWL has also been applied to break other concrements formed inside the patient's body, such as pancreatic, gallbladder, and salivary stones. Its goal is to pulverize the stones with minimum damage to the surrounding tissues and organs.

A few years after the historical introduction of the *Human Model 3* (*HM3*) extracorporeal lithotripter (Dornier MedTech GmbH, Wessling, Germany), the so-called second-generation lithotripters appeared on the market. Representative examples of these lithotripters were the *Piezolith 2300* (Richard Wolf GmbH, Knittlingen, Germany) and the *Lithostar* (Siemens Healthcare GmbH, Erlangen, Germany). Second-generation lithotripters had shock wave sources with a larger aperture. This allowed SWL treatments to be performed using only intravenous sedation. Furthermore, second-generation lithotripters used small water baths or water cushions instead of a huge water tub to couple the shock waves into the patient. Third-generation multifunctional lithotripters, that produced high peak pressures and had relatively small focal sizes followed; however, the first clinical results of a wide-focus

Fig. 5.1 Manufacture of extracorporeal shock wave lithotripters at Storz Medical AG, in Tägerwilen, Switzerland

and low-pressure lithotripter, published in 2002 by Eisenmenger et al. (2002) turned the interest of some manufacturers back to lithotripters with broad focal volumes (Pishchalnikov et al. 2013). As explained later in this chapter, after so many years of SWL there is still no consensus on the optimal focal size and pressure waveform.

Today, there are thousands of extracorporeal lithotripters (also referred to as extracorporeal lithotriptors) in use. Serial manufacturing of a variety of models is a routine in a large number of companies worldwide (Fig. 5.1). Many aspects, such as design, price, available budget, hospital facilities, maintenance costs, service offered by the manufacturer, technical specifications, imaging system, radiation exposure, fragmentation efficiency, multifunctionality, shock wave source, patient population, anesthesia requirements, previous experiences of colleagues, and published clinical results, should be carefully analyzed by a committee of experts before buying a new lithotripter. A lithotripter that may be ideal for a certain lithotripsy center may not be so for another one; however, from most of the extracorporeal lithotripters on the market, excellent results may be obtained, as long as they are used properly by a well-trained urologist with interest in SWL, and if there is an adequate patient selection and treatment protocol (Hanna 2013).

Extracorporeal lithotripters may differ in several aspects; however, all of them mainly consist of a shock wave source, that is, an electro-acoustic transducer, ultrasound and/or fluoroscopy imaging, a coupling device, and a patient treatment table (Fig. 5.2) (Evan et al. 2004; Bailey et al. 2006; Cleveland and McAteer 2007; Lingeman 2007; Loske 2007; Rassweiler et al. 2010; Semins and Matlaga 2010; Tailly 2012, 2013a; Tiselius 2013a). Most lithotripters are modular systems featuring shock wave coupling via a water cushion, multifunctional usage for diagnostics, and urologic interventions with an X-ray C-arm, image processing, and touchscreen user interfaces. Some lithotripters have localization systems that do not

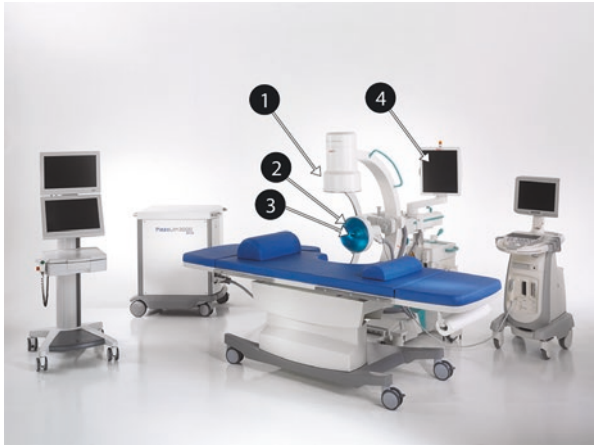


Fig. 5.2 Photograph of the *Piezolith 3000 plus* (with triple focus), showing (*1*) the X-ray image intensifier, (*2*) the isocentric shock wave source, (*3*) the in-line ultrasound scanner, and (*4*) the X-ray monitor. (Courtesy of Richard Wolf GmbH, Knittlingen, Germany)

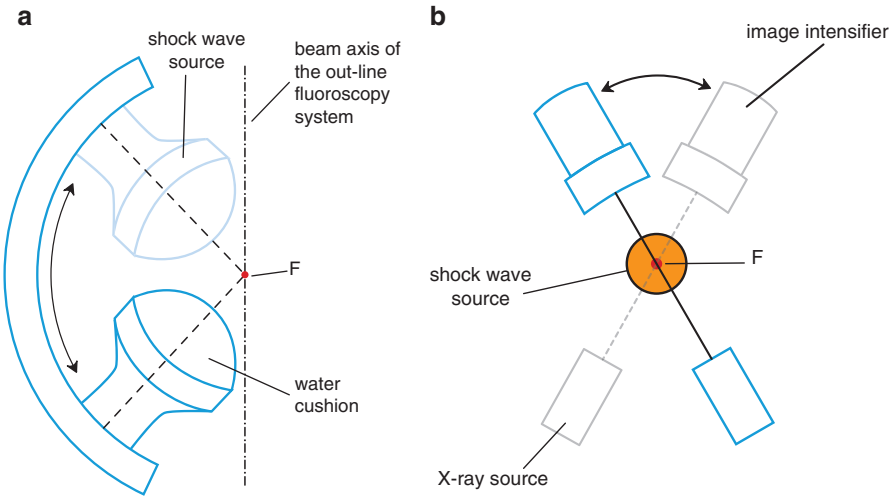


Fig. 5.3 Sketch of the isocentric system configuration of (**a**) the shock wave source and (**b**) the fluoroscopy system of a *Piezolith 3000* extracorporeal lithotripter. (Richard Wolf GmbH, Knittlingen, Germany)

require a mechanical link to the therapy head. Furthermore, isocentric systems are popular, i.e., configurations where the shock wave beam axis and the X-ray or ultrasound beams have a common focus (Figs. 5.3 and 5.4). In many lithotripters it is the patient treatment table that moves and not the shock wave source. X-ray transparent tables allow movement in all spatial axes to place the stone in the focus of the shock wave source. Many extracorporeal lithotripters are multifunctional workstations designed not only for SWL but also for endourological procedures, such as placing a stent or doing an URS.

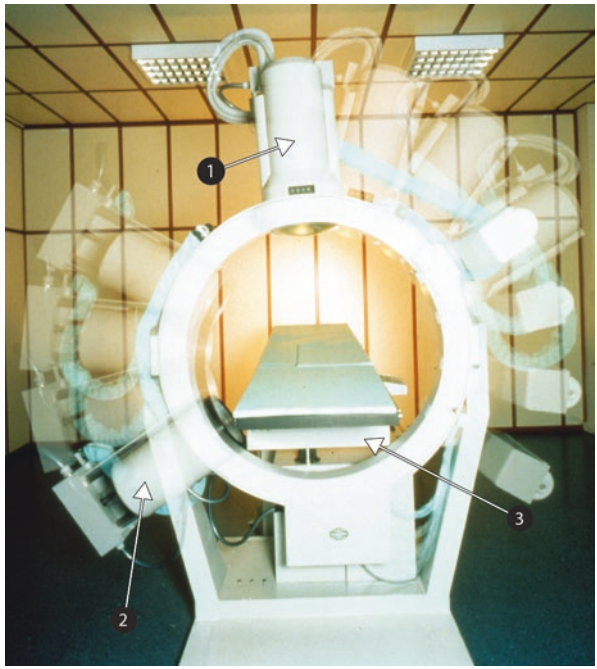


Fig. 5.4 Photograph of the *Lithoring* electrohydraulic lithotripter, one of the first devices with an isocentric design, showing (*1*) the shock wave source, (*2*) the fluoroscopy system, and (*3*) the xyz multifunctional treatment table. (Courtesy of MEDAS s.p.a., Genoa, Italy)

After aligning the system, properly positioning the patient and targeting the stone, shock waves are generated extracorporeally, enter the body with little attenuation through a water bath or a water-filled cushion, get focused on the calculus, and fracture it. Normally several hundred to a few thousands of shock waves are needed to comminute a stone completely. In urological SWL, stone debris passes through the urinary tract and the patient may return to his normal life in less than 48 h after shock wave treatment. The time to complete clearance of all fragments will depend on the stone size and location. As explained in Chap. 4, calculi fracture mainly by spallation, shear, circumferential compression, and cavitation. Depending on the lithotripter, generally between approximately 2000 and 4000 shock waves are administered per session at a rate between 0.5 and 2 Hz (Bailey et al. 2006).

The shock wave source is the main element of a lithotripter. Its design influences important aspects, such as the running costs, the efficiency, the potential tissue damage, and the anesthesia needs. All shock wave emitters have advantages and disadvantages, which may vary depending on their specific use and the system in which they are installed. Most clinical devices use electrohydraulic, electromagnetic, or piezoelectric shock wave sources. Some of them are self-focusing and others use focusing devices, such as acoustic lenses or rigid reflectors. Special shock wave sources and experimental lithotripters, some of them with interchangeable reflectors, have also been designed for research purposes (Figs. 5.5, 5.6, 5.7, and 5.8) (Coleman et al. 1989; Prieto et al. 1991; Cleveland et al. 2000a; Lukes et al. 2012a;

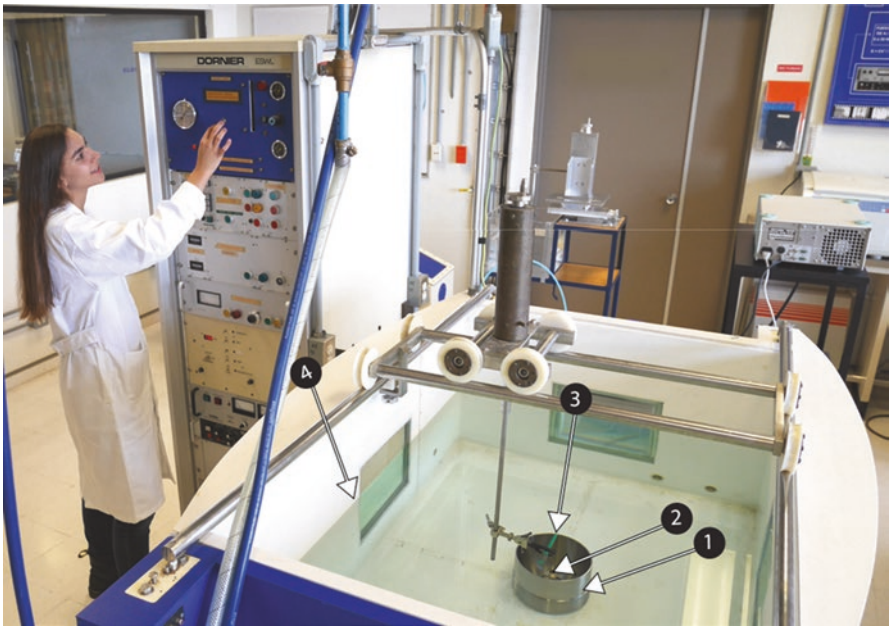


Fig. 5.5 Photograph of the electrohydraulic research shock wave generator at the Shock Wave Laboratory, Center for Applied Physics and Advanced Technology, UNAM, showing (*1*) the stainless steel ellipsoidal reflector, (*2*) the spark-plug, (*3*) the clamp fastened to the xyz positioner, and (*4*) the water level. The upper part of the control console belongs to the *HM3* shock wave generator shown in Fig. 5.9, and the lower part houses the controls for the device shown here. (Photograph: F. Fernández)

Fig. 5.6 Stainless steel reflectors with different shapes (ellipsoidal and parabolic), designed to be used in the shock wave source shown in Fig. 5.5

Oshita et al. 2014). These systems have been very useful to study shock wave propagation through different materials including tissue and cell cultures, to record pressure profiles, use high-speed photography to study cavitation and stone phantom

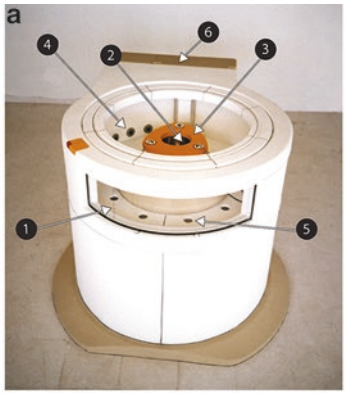


Fig. 5.7 (**a**) Photograph of an electrohydraulic research shock wave generator at the Shock Wave Laboratory, Center for Applied Physics and Advanced Technology, UNAM, showing (*1*) the water tank with its viewing window, (*2*) the stainless steel reflector, (*3*) the support for the laser pointers, (*4*) the water inlets, (*5*) the water outlets, and (*6*) the control panel. For clarity, the xyz positioner used to place the samples inside the pressure field was not included. (**b**) Photograph of the ellipsoidal stainless steel reflector with three adjustable laser pointers. (Design and photographs: S. Tacher)

comminution, as well as to perform a variety of in vitro, ex vivo, and in vivo experiments under well-controlled laboratory conditions.

A large amount of the animal and human studies reported in the literature have utilized the experimental Dornier *XL1* or the clinical *HM3* lithotripter. Because of the popularity of the initial Dornier shock wave sources, several experimental devices were designed to mimic the pressure profile produced by the *HM3* (Fig. 5.8) (Coleman et al. 1989; Prieto et al. 1991; Cleveland et al. 2000a; Loske et al. 2003). Other research groups modified standard shock wave sources or adapted them to experimental lithotripters (Figs. 5.9 and 5.10) (Zhong et al. 1997b, 1999b, 2011; Xi and Zhong 2000; Zhong and Zhou 2001; Loske and Prieto 2002; Loske et al. 2002b, c, 2003; Zhou et al. 2004b; Pierre et al. 2008; Fernández et al. 2009b). Small water tanks, coupled to commercial shock wave sources to evaluate their performance or to study a variety of shock wave-induced phenomena, are also common (Fig. 5.11).

This chapter will mainly deal with SWL in urology, because of the popularity and high success rate of shock waves to comminute urinary stones; however, SWL for gallbladder, pancreatic, and salivary gland stones will also be discussed. The purpose is to provide an overview of the shock wave generation methods that are used in SWL. Beyond a description of technical details (which may be consulted in

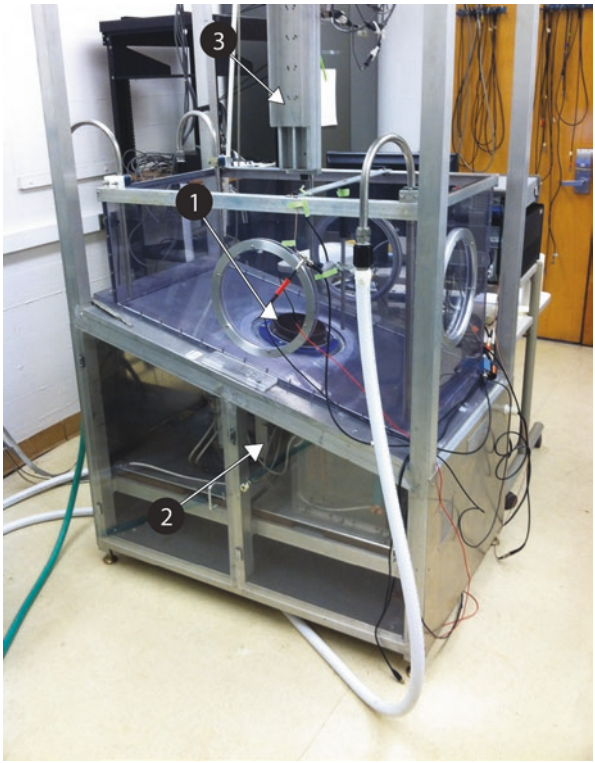


Fig. 5.8 Photograph of the *HM3*-based research lithotripter at the Applied Physics Laboratory, University of Washington, Seattle, USA, showing (*1*) the ellipsoidal reflector, (*2*) the capacitor charging unit, and (*3*) the xyz positioner. (Courtesy of M. Bailey)

the references listed at the end of the book or obtained directly from the manufacturers of SWL equipment), the aim is to inform the unfamiliar reader of the physical phenomena involved and the most important developments that have arisen ever since the very first clinical applications of shock waves.

Some of the technologies mentioned in this section were never actually transferred to the industry, and only remained as experimental devices. Despite that, their description was included, because they may result of interest from the basic science point of view, and stimulate the development of new systems and applications. Several components of the described equipment such as ultrasound scanners, X-ray C-arms, and treatment tables may not be exclusive of a single shock wave generator. Only one or two representative lithotripters could be included for each shock wave generation principle. Old models, that due to their historical importance may be considered as part of the "general culture" of anyone whose work is related to biomedical application of shock waves, were also described. Recommendations to perform SWL are provided, most of them based on the physics of shock wave generation. Some of the methodologies and equipment still on a stage of research are also commented. The latter is not only for the purpose of informing the reader, but also to encourage him to contribute with innovative ideas to the development of safer and more efficient therapies.

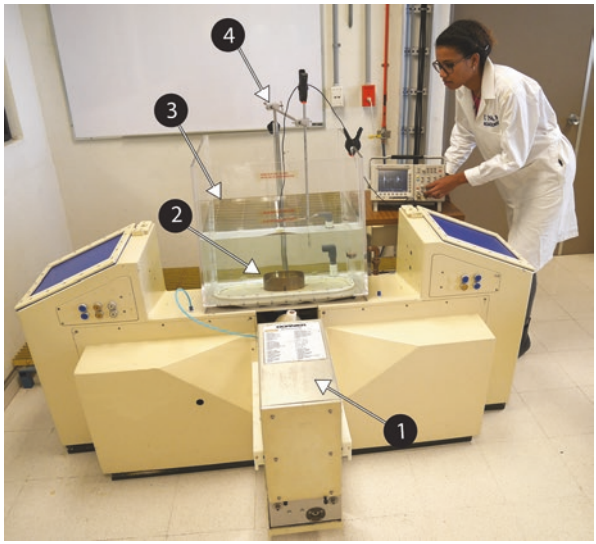


Fig. 5.9 Photograph of the *HM3*-based (Dornier MedTech GmbH, Wessling, Germany) research lithotripter at the Shock Wave Laboratory, Center for Applied Physics and Advanced Technology, UNAM, showing (*1*) the shock wave generator, (*2*) the ellipsoidal reflector, (*3*) the water level, and (*4*) the xyz positioner. (Photograph: F. Fernández)

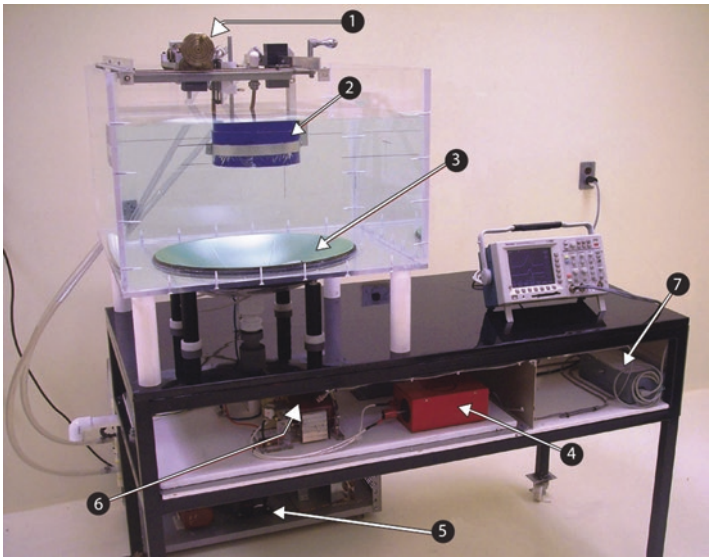


Fig. 5.10 Photograph of the *Piezolith 2501*-based (Richard Wolf GmbH, Knittlingen, Germany) research shock wave source at the Shock Wave Laboratory, Center for Applied Physics and Advanced Technology, UNAM, showing (*1*) the xyz positioner, (*2*) the thermally insulated water cooling coil, (*3*) the piezoelectric shock wave source, (*4*) the spark-gap driver, (*5*) part of the water cooling system, (*6*) the capacitor, and (*7*) the pulse generator. (Photograph: F. Fernández)

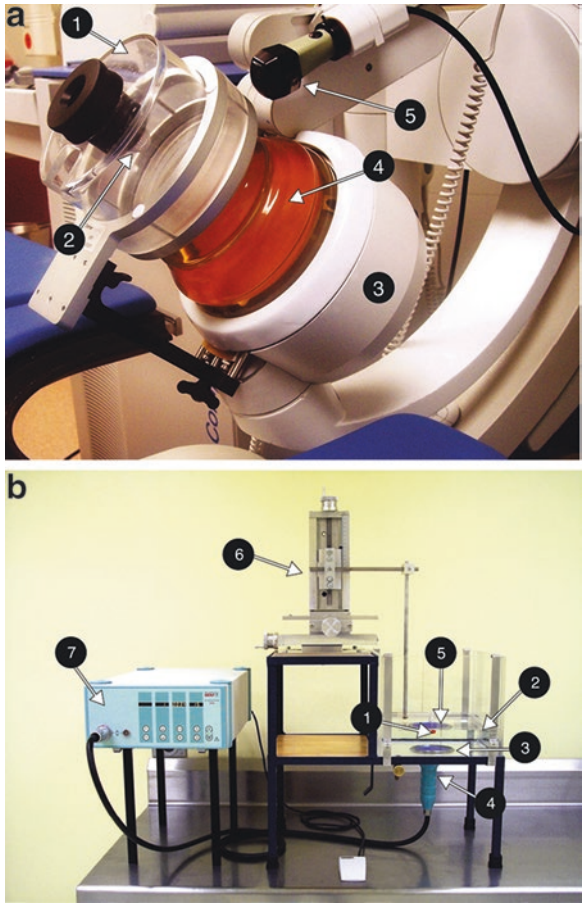


Fig. 5.11 (**a**) Photograph of a *Compact Sigma* shock wave lithotripter (Dornier MedTech GmbH, Wessling, Germany), showing (*1*) a small water test tank, (*2*) a mesh to place kidney stone phantoms inside the water tank, (*3*) the shock wave source, (*4*) the water cushion, and (*5*) the ultrasound scanner. (**b**) Photograph of an experimental device based on a *Piezoson 100 Plus* (Richard Wolf GmbH, Knittlingen, Germany) shock wave unit showing (*1*) a vial placed at the focus inside the water tank, (*2*) the water level, (*3*) the coupling membrane, (*4*) the shock wave source, (*5*) the reflection of the coupling membrane on the water surface, (*6*) the xyz positioner, and (*7*) the power supply and control unit. (Photograph: F. Fernández)

Despite the release of a large amount of shock wave sources and lithotripters, there is still basic research to do in order to fully understand the phenomena responsible for stone comminution and tissue damage during SWL, improving treatment outcomes, and reducing re-treatment rates.

5.2 Electrohydraulic Lithotripters

The first shock wave source used for clinical applications was electrohydraulic. As mentioned in Chap. 2, the idea of producing focused underwater shock waves for medical applications by high-voltage electric discharges at one focus of a paraellipsoidal metallic reflector was conceived long before the introduction of SWL (Rieber 1947). Nowadays, single spark-gap shock wave sources and twin spark-plug devices are used in various clinical applications and research.

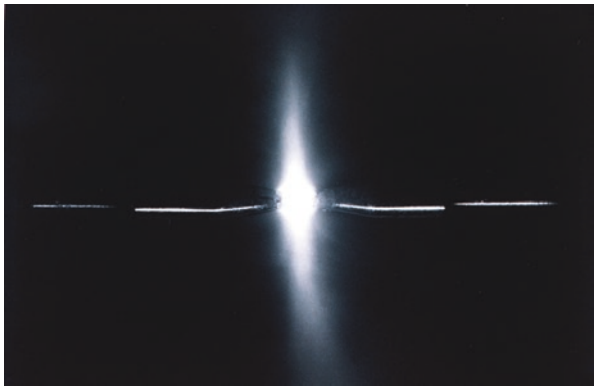


Fig. 5.12 Photograph of a high-voltage discharge between two electrodes immersed in water. (Photograph: A. Sánchez)

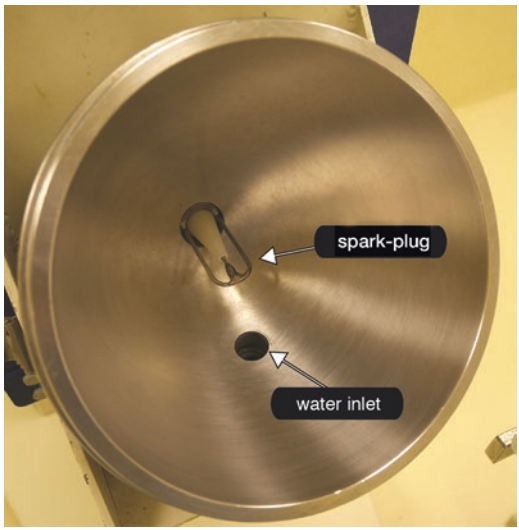


Fig. 5.13 Photograph of the ellipsoidal reflector and spark-plug of a *Breakstone 100* (Breakthrough Medical Corp., Gaithersburg, Maryland, USA) extracorporeal shock wave lithotripter

5.2.1 Single Spark-Gap Shock Wave Sources

Electrohydraulic shock wave generators produce underwater shock waves by electrical breakdown (15–30 kV) between two electrodes immersed in water (Fig. 5.12), located at the focus (*F1*) closest to a paraellipsoidal metallic reflector (Fig. 5.13). A high-voltage power supply stores the energy in a set of capacitors (normally between 40 and 100 nF) in order to abruptly discharge them across the underwater spark-gap by means of a trigger switch. Dielectric breakdown occurs and a fast expanding plasma bubble is generated at temperatures of approximately 20,000 degrees Kelvin. This is accompanied by an intense emission of visible light and ultraviolet radiation (Fig. 5.14).

Fig. 5.14 High-speed photographic sequence (156.8 μs between images) of an underwater electric discharge between two electrodes (capacitance 80 nF, voltage 16 kV). The sequence starts at the upper left corner and continues from left to right until it ends at the lower right corner. (Photograph: E. Fernández)

During a very short lag time, the current between the electrodes is low until the voltage at the spark-plug suddenly drops due to the electrical breakdown of the water. Depending on the properties of the water and the shape of the electrodes, the lag time can vary significantly from one discharge to the next. The plasma

expansion generates an almost spherical shock front, which is isotropically radiated from *F1* reflected off the reflector and focused on the second focus, normally referred to as *F2* (Fig. 3.5). Since the acoustic impedance of a material is related to the reflected energy, reflectors for SWL are generally made out of materials with high acoustic impedance, such as brass or stainless steel.

The peak electric current of the underwater discharge is very high (10–20 kA) and mainly depends on the released energy and the inductance of the circuit. A shock wave is generated almost from the onset of plasma formation. Most of the electrical energy is lost due to the mechanical work required to generate the shock front, as well as in the form of radiation. A much smaller amount of energy is lost by thermal conduction. It has been estimated that in extracorporeal electrohydraulic lithotripters, only approximately 5 % of the total energy stored in the capacitors reaches the kidney stone (Coleman and Saunders 1989). Since the electrical breakdown depends on the conductance of the water between electrodes, it is advisable to adjust the conductivity of the water inside shock wave source as indicated by the manufacturer.

The design of the ellipsoidal reflector is crucial for many reasons. One of them is that its shape is related to pain: larger apertures produce less pain at the shock wave entrance site. First generation shock wave sources had ellipsoidal reflectors with semiminor axis to semimajor axis ratios between 0.5 and 0.6. To reduce pain, reflectors of second-generation lithotripters were designed to have ratios of approximately 0.75. The physics of the reflection of a spherical shock wave off a rigid ellipsoidal surface are complex; however, assuming that the reflection coefficient does not depend on the incident angle provides good approximations to calculate the energy density in the focal zone.

Shock wave sources (not only electrohydraulic) store electrical energy in a set of capacitors, because a large amount of energy is required in a short time. The energy E (in joules) stored in a capacitor can be calculated by $E = 0.5CU^2$, where U is the voltage in volts (V) and C is the capacitance of the capacitor in farads (F). There is a relationship between this energy and the energy of the shock wave; however, the electrical energy delivered to the spark-gap should not be used directly as a measure of shock wave "efficiency" or "power."

After a single dielectric breakdown, more than one shock wave is generated. A small part of the diverging, non-reflected shock front (Fig. 3.8) arrives at *F2* before the reflected pulse. The contribution of this direct pressure pulse to fracture calculi is not significant. The reflected shock wave reaches *F2* after the leading non-reflected wave and is followed by another non-reflected and reflected pulse, produced by the plasma bubble collapse at *F1*. In the Dornier *HM3*, the delay between the direct and the reflected shock wave was approximately 30 μs. There is evidence that the initial focused shock wave is responsible for most of the calculi disintegration. Additional shock waves originated by the violent collapse of cavitation bubbles at *F2* have also been recorded (Bailey et al. 2005; Pishchalnikov et al. 2005; Chitnis and Cleveland 2006). These signals, produced by bubble collapses close to the focal spot, are not exclusive of electrohydraulic lithotripters.

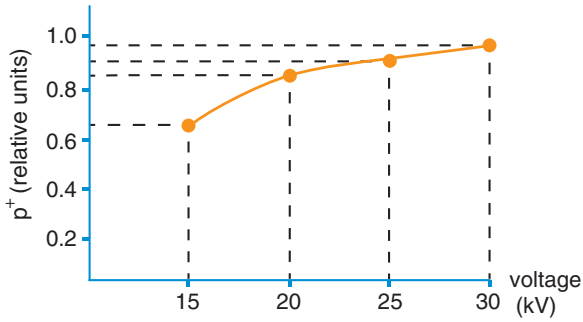


Fig. 5.15 Discharge voltage versus generated peak-positive pressure at the focal spot of an electrohydraulic lithotripter

Electrohydraulic shock wave sources emit broadband pressure pulses with very short durations. The focal zone may slightly vary in position and shape depending on the discharge voltage. This should not be a major concern for most biomedical uses, because the focal zone of these devices is relatively large. An increase in voltage will produce a decrease in the rise time (t_r) of the shock wave. The relationship between discharge voltage and peak-positive pressure (p^+) is not linear. When increasing the voltage, p^+ initially rises rapidly; however, at voltages above approximately 20 kV, as the voltage is raised, the pressure increases slowly (Fig. 5.15). In vitro stone phantom fragmentation showed that increasing the generator voltage from 16 to 20 kV enhanced stone fragmentation efficiency regardless of the physical properties of the stone; however, increasing the voltage from 20 to 24 kV did not result in a significant improvement (Loske 2010).

The pressure profile of the shock wave coupled into the patient and, as a consequence, treatment efficiency, pain, and tissue damage depend to a certain extent on the design of the reflector, the discharge voltage, the capacitance, the inductance of the circuit, the water conductivity, the coupling device, and the shape of the electrodes (Loske and Prieto 1993; Bailey et al. 1998, 1999). Electrohydraulic devices produce shock waves with shorter rise times than piezoelectric or electromagnetic sources. Rise times have been measured to last approximately 30 ns; however, this value is believed to be overestimated due to the limitations of the hydrophones. Theoretically, the rise time of an electrohydraulic shock wave source could be less than one nanosecond (Chitnis 2002). As mentioned, the high-voltage discharge between the electrodes at *F1* generates intense visible light and ultraviolet (UV) radiation with a peak between approximately 55 and 150 nm. In most extracorporeal lithotripters this radiation is almost completely blocked by the water inside the reflector and the membrane covering the shock wave source.

Advantages of electrohydraulic shock wave sources are the high plasma expansion velocity produced by the electric breakdown, the relative simple design, and its low cost. Further advantages of lithotripters using spark-gap shock wave sources are their high disintegration efficiency and low re-treatment rate. Disadvantages are the noise produced by the high-voltage electric breakdown and the need to replace the spark-plug because of erosion of the electrode tips. Protective headphones should

be worn by the patient and the lithotripter operator. The small aperture of some electrohydraulic shock wave sources, i.e., the narrow shock wave entry site at the patient's skin, may originate pain. Moreover, it should be considered that the electric breakdown between electrodes generates a relatively strong electromagnetic field that in some rare cases could cause arrhythmia. Because of this, spark-gap lithotripters are sometimes gated to the cardiac cycle of the patient. Deviations of p^+ at *F2* of up to 30 % (Fig. 5.16) produced because of spark jitter (Coleman and Saunders 1989; Prieto et al. 1991) are also considered as disadvantages; however, since hundreds of shock waves are needed in most clinical treatments, pressure variations are averaged and not too relevant.

As mentioned before, the Dornier *HM3* extracorporeal shock wave lithotripter (Figs. 2.8 and 2.9) was the first clinical device of its kind. Commonly referred to as

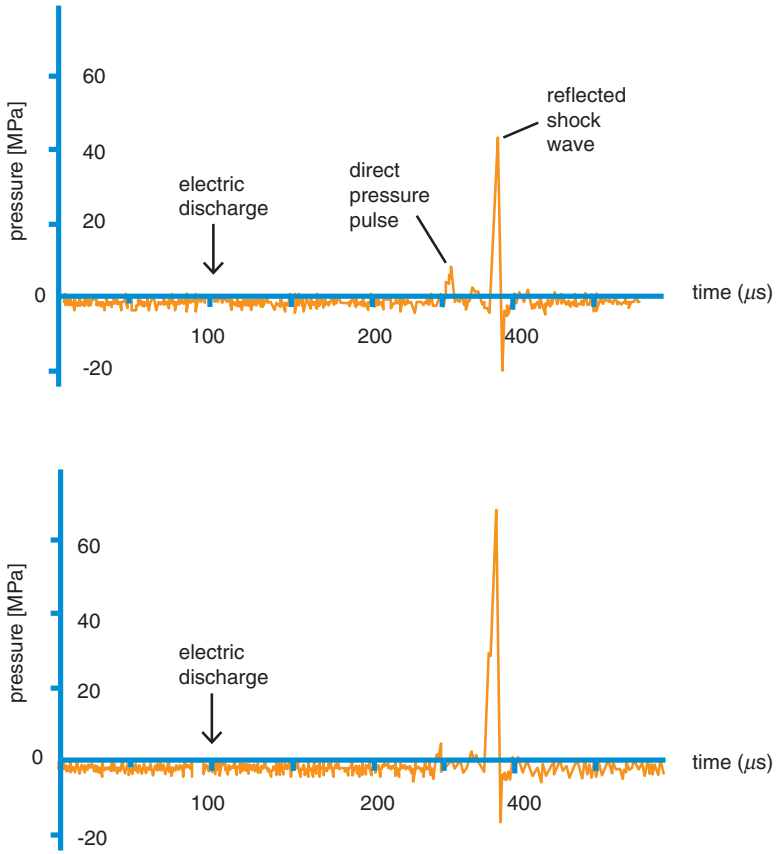


Fig. 5.16 Two pressure records obtained with a PVDF pressure hydrophone from consecutive shock waves produced at the same discharge voltage by an electrohydraulic shock wave source. The arrow indicates the instant when the spark-gap was fired

Fig. 5.17 Photograph of the water treatment plant (Wiegand GmbH, Ettlingen, Germany) used to deionize and degas the water of an *HM3* lithotripter (Dornier MedTech GmbH, Wessling, Germany), showing (*1*) the degasser tank, (*2*) the deionization tank, (*3*) the degasser motor that pumps water to the tub, (*4*) the vacuum motor and the pump that creates vacuum in the degasser tank, (*5*) the mixing valve, (*6*) the input valve to the degasser tank, (*7*) the output to the tub, and (*8*) the water filter. (Photograph: F. Fernández)

"the gold standard," it was the most used extracorporeal lithotripter for many years (Cass 1995; Preminger 1995; Lingeman 1996; Lingeman and Safar 1996; Graber et al. 2003; Gronau et al. 2003; Gerber et al. 2005; Loske 2007). The *HM3* has now been replaced by smaller, cheaper, and easier to use lithotripters. Nevertheless, it remains a reference standard and, according to several authors, many newer lithotripters have not reached the stone-free rates of the *HM3* (Chan et al. 1995; Fuselier et al. 1999; Teichman et al. 2000; Graber et al. 2003; Lingeman et al. 2003; Portis et al. 2003; Gerber et al. 2005; Weizer et al. 2007; Argyropoulos and Tolley 2007; Bach and Buchholz 2011). It is surprising that so many years after its introduction into the market, there were still reports comparing the *HM3* with modern lithotripters (Zehnder et al. 2011). This first lithotripter was a huge device, consisting of a water tub filled with deionized and degassed water by a special water treatment plant (Fig. 5.17), a patient stretcher, and an electrohydraulic shock wave source. Stone localization was achieved using two X-ray systems arranged at an angle of 90°. Even if the *HM3* was a very successful lithotripter, it had drawbacks, such as the need of two X-ray units, the large water bath, and expensive spark-plugs. C-arm fluoroscopy systems, small water-filled cushions to couple the shock waves into the patient, and shock wave sources based on other physical principles were proposed as solutions. SWL with the *HM3* was performed under general or spinal anesthesia, because the small aperture of the reflector (140 mm) and the relative high pressure values resulted in high energy densities at the skin and shock wave path. The modified version of the *HM3* and the *HM4* had a weaker shock wave generator and a reflector with a larger aperture (170 mm), so that most treatments could be performed using

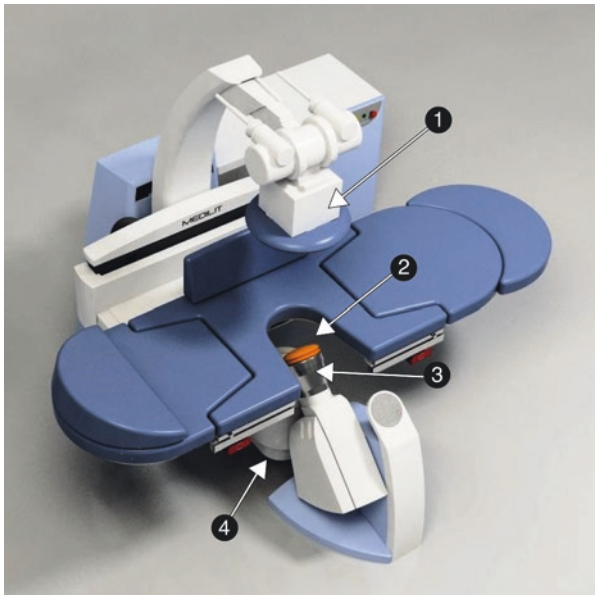


Fig. 5.18 Image of a *Medilit* lithotripter, showing (*1*) the X-ray source, (*2*) the water cushion, (*3*) the ellipsoidal reflector, and (*4*) the image intensifier. (Courtesy of Medipo ZT s.r.o., Brno, Czech Republic)

sedoanalgesia (Graff et al. 1988b). The *HM4* (Fig. 2.10) was the last lithotripter of the Dornier *Human Model* series (Tailly 1989, 1990, 1999). It required less space, because it had a water cushion instead of the water tub to couple the shock waves into the body.

A typical modern electrohydraulic lithotripter is the *Medilit*, manufactured by Medipo ZT s.r.o., Brno, Czech Republic (Figs. 5.18 and 5.19). The device was designed for SWL of urinary, gallbladder, and common bile duct stones, but patients suffering from various orthopedic conditions can also be treated. The entire procedure is computer-controlled and operated from a control room, protecting the staff from radiation and the noise produced by the electric discharges. Both X-ray and ultrasound imaging can be operated simultaneously, reducing the radiation dose during continuous treatment monitoring. Shock wave generation is synchronized by the R-wave of the electrocardiogram (ECG) and may also be synchronized with the patient's respiration. The water inside the water cushion is degassed and heated. To compensate for the wear of the spark-plug, the gap between electrode tips is adjusted via a computer-driven mechanism. Each spark-plug can be used to treat several patients and be refurbished at low cost. As in many other lithotripters, to localize the stone in three dimensions, two different radiographic projections are obtained. After this, the stone is highlighted on the monitor by using the cursor and the patient is automatically moved into the correct position. The first commercial series was the *Medilit M5*; however, the most common lithotripter in the Czech Republic has been the *M6* (Král et al. 2010). The *M7* is also in use and a new version (*M8*) will be released soon. The models mainly differ in the level of comfort and ease of operation; however, all versions share the same shock wave source developed at the Institute

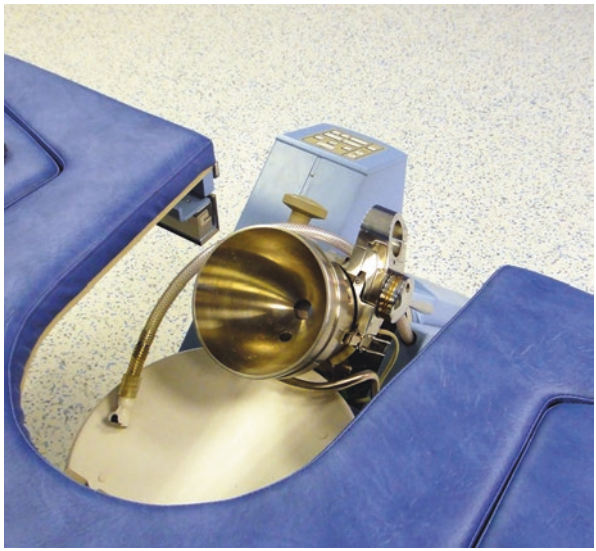


Fig. 5.19 Photograph of the shock wave source of a *Medilit* lithotripter, showing the ellipsoidal reflector without the spark-plug and without the water cushion. (Courtesy of Medipo ZT s.r.o., Brno, Czech Republic)

of Plasma Physics of the Academy of Sciences of the Czech Republic in the late 1980s. The discharge voltage can be varied continuously from 5 to 15 kV. At the maximum voltage, p^+ equals approximately 50 MPa. The −6 dB focal volume has the shape of a cigar with a 9 mm diameter and a length of 38 mm. The focal length of the shock wave source is 140 mm. These measurements were obtained by the manufacturer according to the standard of the IEC (International Electrotechnical Commission).

Jena Med Tech GmbH (Jena, Germany) developed the *LithoSpace*, an electrohydraulic shock wave source with an innovative design (Fig. 5.20) (Hartung and Schwarze 2010). The compact and versatile shock wave head can be coupled to almost any surgical table and C-arm without a mechanically rigid connection. After treatment, the system may be folded into a "park position" and moved away. Both X-ray and ultrasound real-time visualization are possible. To couple the shock wave head to the X-ray C-arm, an optical marker panel is mounted on the image intensifier (Fig. 5.21). The stereo camera detects the light reflected by another optical marker panel mounted on the *LithoSpace* and the one on an X-ray C-arm. A computer calculates the position of the shock wave head relatively to the imaging device. A similar arrangement can be used for ultrasound imaging (Fig. 5.22). The electrohydraulic shock wave source offers one of the largest −6 dB focal zones on the market (160 × 20 × 20 mm). According to the manufacturer, the peak pressures p^+ and p^- can be varied from approximately 26 to 38 MPa and from −3.6 to −5.0 MPa, respectively. These measurements were obtained with a fiber-optic probe hydrophone (FOPH) model *500* (RP Acoustics, Leutenbach, Germany). Shock waves can be generated at rates between 0.5 and 5 Hz. The penetration depth of up to 220 mm allows treatment of obese patients. Extracorporeal shock wave therapy (ESWT)

Fig. 5.20 Photograph of the basic version of the *LithoSpace* in its undertable position, showing (*1*) the touch panel, (*2*) the coupling pressure indicator, (*3*) the water cushion, (*4*) the stereo camera, (*5*) a superimposed therapeutic volume on the X-ray image, (*6*) the reflector panel, and (*7*) the shock wave source. (Courtesy of Jena Med Tech GmbH, Jena, Germany)

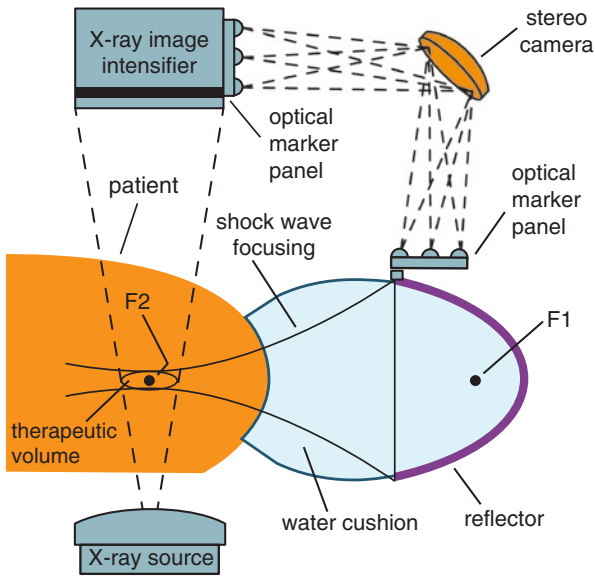


Fig. 5.21 Schematic showing the touchless coupling of a *LithoSpace* shock wave source (Jena Med Tech GmbH, Jena, Germany) with an X-ray C-arm. To assure that the stone is located in the focal volume, infrared waves are sent by the stereo camera system and are reflected by the optical markers fixed on the image intensifier panel and on the shock wave source

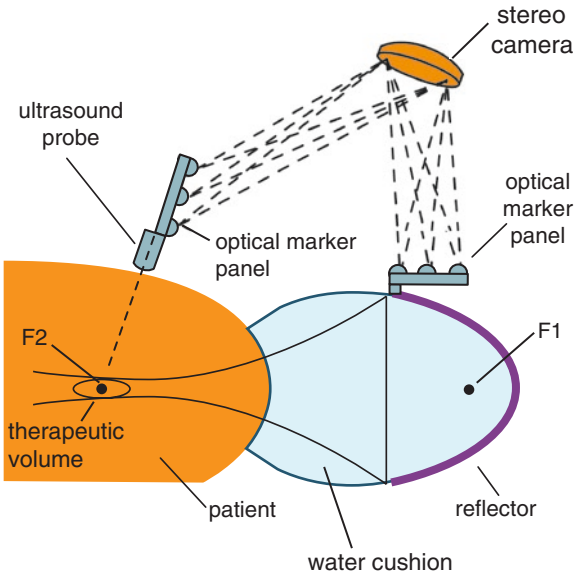


Fig. 5.22 Schematic of the arrangement to position the stone in the focal volume of a *LithoSpace* shock wave source (Jena Med Tech GmbH, Jena, Germany) using ultrasound imaging

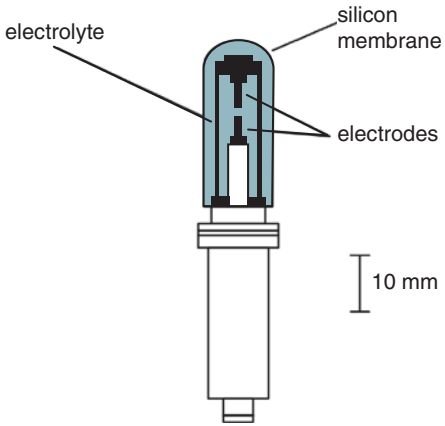


Fig. 5.23 Schematic of an electroconductive spark-plug as designed by Cathignol and colleagues (1991)

such as treatment of necrotic femur heads, tennis elbows, heel spurs, and calcified shoulders are also possible with the *LithoSpace*.

To lengthen the life span of the electrodes, the so-called electroconductive spark-plugs have been developed (Cathignol et al. 1991; Bourlion et al. 1994). If the electrodes are immersed in an electrolyte, i.e., a highly conductive degassed aqueous solution of sodium chloride (NaCl), instead of degassed water, the energy is delivered into the medium in a shorter time, because the latency time and the amplitude of the oscillations of the discharge current decrease. The electrodes and the electrolyte are encased in a silicone membrane (Fig. 5.23). The remaining part of the circuit is analogous to that of the aforementioned electrohydraulic shock wave sources.

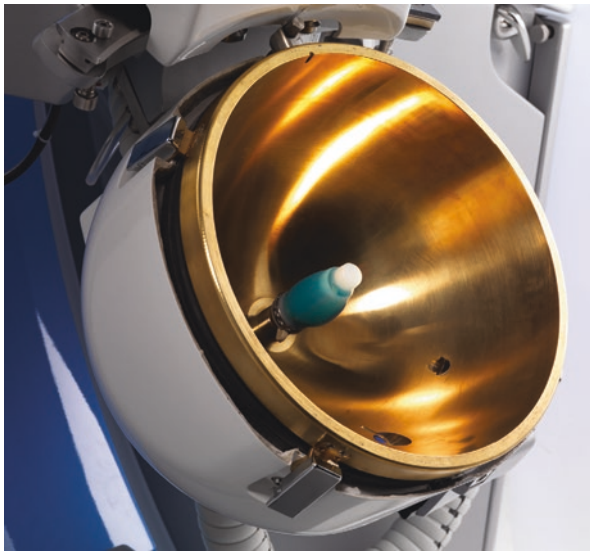


Fig. 5.24 Photograph of the ellipsoidal reflector and the electroconductive spark-plug of a *Sonolith i-sys* lithotripter. (Courtesy of EDAP TMS, Vaulx-en-Velin, France)

Advantages compared to standard electrohydraulic spark-plugs are that shock wave generation always occurs at the same spot and that the pressure range is less restricted. Furthermore, the wear of the electrode tips is reduced by a factor of approximately 50, compared with standard electrohydraulic spark-plugs (Cathignol et al. 1991). Since the electrical discharge does occur in a well-controlled electrolytic solution, the process is not dependent on the water quality inside the shock wave head (Fig. 5.24). According to Broyer et al. (1996), the electro-acoustic efficiency increases from approximately 5.5 % for standard electrohydraulic spark-plugs to 11 %. SWL performed using these improved spark-plugs is sometimes also referred to as electroconductive lithotripsy (ECL). The first extracorporeal lithotripter with an electroconductive shock wave source (*Sonolith*) was developed by Technomed Medical Systems (Vaulx-en-Velin, France) in collaboration with the French National Institute of Health and Medical Research (INSERM). It was followed by the *Sonolith Vision*, which showed to produce fine stone fragmentation and low re-treatment rates compared to other lithotripters (Pemberton and Tolley 2006). According to Nomikos and colleagues (2007) the *Sonolith Vision* achieved a higher stone-free rate (SFR) than reported by Cass (1995) using the unmodified *HM3* for single renal calculi.

Two modern representative lithotripters based on electroconductive technology are the *Sonolith i-sys* (Fig. 5.25) and the compact *Sonolith i-move* (Fig. 5.26), launched on the market in 2007 and 2010, respectively by EDAP TMS (Vaulx-en-Velin, France). The solution inside the electroconductive spark-plugs allows electrode lifetimes of approximately 25,000 shock waves and accurate electrical discharges, generating a repeatable focal zone. An automatic pressure regulator permanently adjusts the voltage to deliver the requested pressure, compensating for variations due to the electrode wear. As in most modern lithotripters, the shock wave

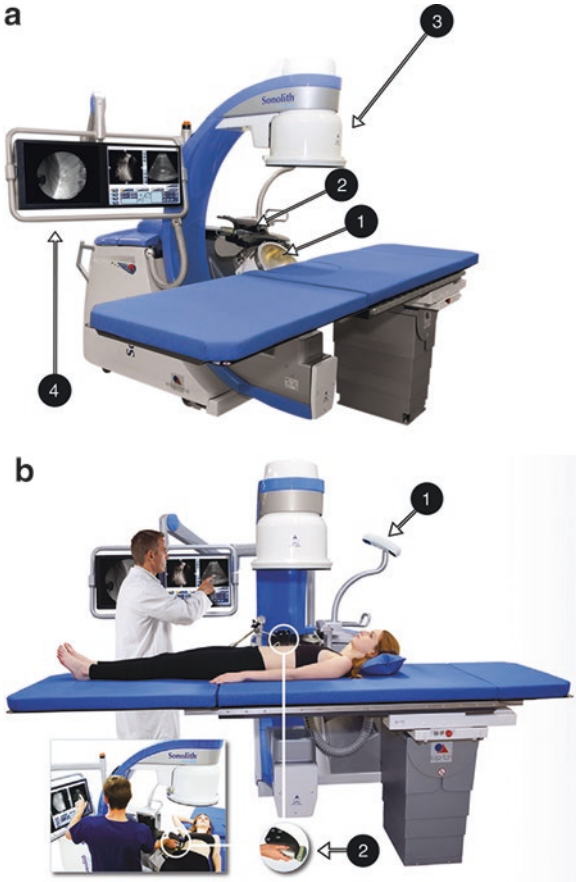


Fig. 5.25 The *Sonolith i-sys* lithotripter. (**a**) Photograph showing (*1*) the shock wave source, (*2*) the ultrasound probe, (*3*) the X-ray image intensifier, and (*4*) the ultrasound and fluoroscopy monitor. (**b**) Photograph showing (*1*) the infrared camera of the *Visio-Track* system and (*2*) the free-line hand-held ultrasound probe. (Courtesy of EDAP TMS, Vaulx-en-Velin, France)

head is covered with a flexible silicon membrane. The focal distance of the *Sonolith i-sys* is 170 mm, but can go up to 210 mm, thanks to the membrane flexibility. This allows treatment of very obese patients. For the *i-move* lithotripter this distance is 10 mm shorter. The aperture of the reflector installed in the *i-sys* is also larger (approximately 290 mm) compared to the *i-move* (approximately 250 mm). The manufacturer reports that the size of the −6 dB focal zone of the *Sonolith i-sys* and the *Sonolith i-move*, measured with a PVDF needle hydrophone according to the IEC 61846 standard, is 3.2×2.6×22.4 mm and 3.5×2.6×35 mm, respectively. Their peak-positive pressure ranges from 111 to 129 MPa (*i-sys*) and from 107 to 144 MPa (*i-move*). In both models, the amplitude of the peak-negative pressure pulse does not exceed 12 MPa. Due to variations in the design of the shock wave sources, the maximum energy flux densities delivered by the two electroconductive lithotripters are slightly different (*i-sys*: 1.27 mJ/mm^2, *i-move*: 1.36 mJ/mm^2). Ultrasound and X-ray imaging can be performed simultaneously. A so-called *Visio-Track* system was implemented in both models in 2010. When using this feature, the stone can be located using a free-line hand-held ultrasound probe (Figs. 5.25b and 5.27).

Fig. 5.26 Photograph of the *Sonolith i-move* lithotripter, showing (*1*) the shock wave source, (*2*) the infrared camera, and (*3*) the ultrasound monitor and 3-D reconstruction of the stone. (Courtesy of EDAP TMS, Vaulx-en-Velin, France)

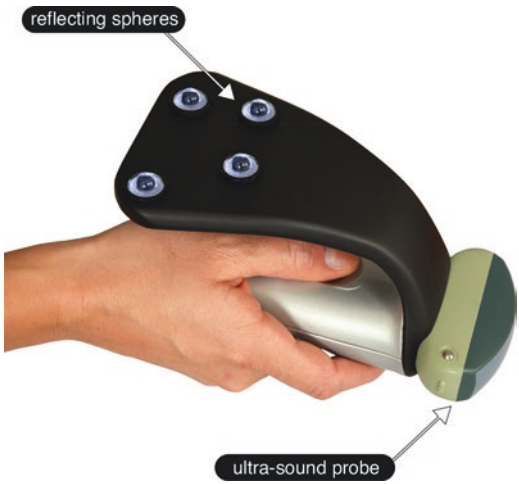


Fig. 5.27 The hand-held ultrasound probe of the EDAP *Visio-Track* system. (Courtesy of EDAP TMS, Vaulx-en-Velin, France)

The position of four small reflecting spheres located on top of the hand-held probe is detected three-dimensionally via infrared stereovision and registered by the computer. After touching the image of the stone on the screen, the treatment table automatically moves until the stone is located at *F2*, decreasing the use of fluoroscopy and reducing X-ray exposure (Abid et al. 2013, 2015). Real-time follow-up maintains the stone at the focal point.

Pressure waves that start with a tensile pulse and are followed by a positive pressure pulse, generated individually or with a delay before or after standard shock waves,

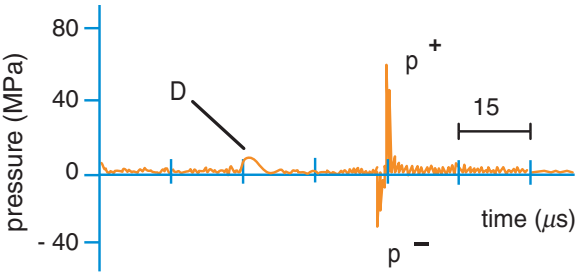


Fig. 5.28 Pressure waveform recorded with a PVDF needle hydrophone at the second focus of the pressure-release reflector of an experimental electrohydraulic shock wave generator. The non-reflected pressure pulse (D) was recorded approximately 30 μs before the reflected negative (p^-) and positive (p^+) pressure pulses

have also been proposed as an option to improve the efficiency of extracorporeal lithotripters (Cathignol 1998). The proposal was promising, because renal calculi are more susceptible to be broken by tensile than by compressive stress (Kaneko et al. 1979). Phase-inverted pressure waveforms (Fig. 5.28) can be obtained with electrohydraulic shock wave sources having a pressure-release instead of a rigid reflector (Müller 1987; Bailey 1997a, b; Bailey et al. 1998, 1999; Loske and Prieto 2002). As explained in Sect. 4.3, reflection at an interface presenting a decrease in impedance to the incoming wave leads to a phase change in the reflected wave. Phase reversal occurs because energy balance must be maintained at the interface between the water and the soft pressure-release material. If negligible energy is lost at the boundary, the sum of the intensity of the reflected and the transmitted waves equals the intensity of the incident wave. Pressure waves from rigid and pressure-release reflectors are similar in amplitude, duration, and rise time, but differ in waveform. Pressure-release reflectors have not been used clinically, but reduced cavitation and tissue injury in animals (Evan et al. 2002).

The usefulness of a single electrohydraulic shock wave source driven by a sequence of two sparks was evaluated in the past (Bailey 1997b). As explained in Sect. 4.7, tandem shock waves can improve SWL outcomes; however, to generate shock waves with a conventional underwater single spark-gap electrohydraulic shock wave generator at delays shorter than 10 ms could not be achieved (Lukes et al. 2015). This was tested using an experimental electrohydraulic shock wave generator implemented with a second capacitor charging unit to generate two discharges at delays between 200 μs and 4.2 ms. Electric discharges using capacitances equal to 40, 80, 120, and 160 nF were used. In the dual-pulse mode, the capacitance was always set equal for both capacitor sets. A high-speed digital camera recorded the underwater electric discharges. The plasma bubble between the electrodes reached its maximum diameter approximately 1.2–2.5 ms after the electric breakdown and required approximately the same amount of time to collapse. Figure 5.29 shows a photographic sequence of two underwater electric discharges

Fig. 5.29 High-speed photographic sequence (160.5 μs between images) of two underwater electric discharges between two electrodes, generated at a delay of 1.56 ms (capacitance 160 nF, voltage 16 kV). The sequence starts at the upper left corner and continues from left to right until it ends at the lower right corner. The first electric discharge occurred shortly before the second image and the second discharge occurred between the 10th and the 11th image. (Photograph: E. Fernández)

generated with a time delay of 1.56 ms. The second discharge occurred before the bubble produced by the first electric breakdown collapsed. Two separated shock fronts could not be generated at delays below 10 ms. Nevertheless, composite reflectors for electrohydraulic shock wave sources can be used to generate tandem

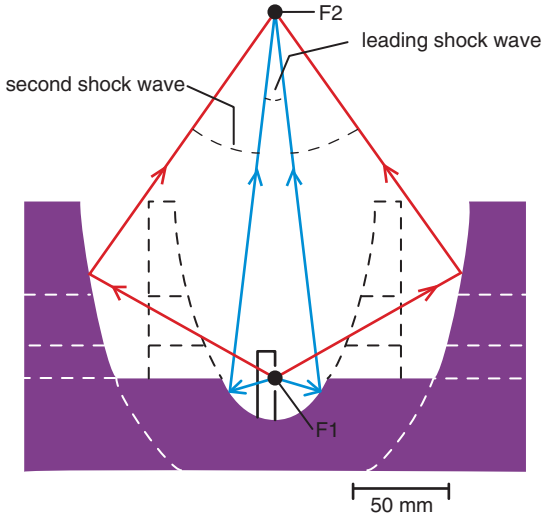


Fig. 5.30 Schematic of a research electrohydraulic shock wave source with a double reflecting ellipsoidal surface, designed by Zhong et al. (1997b)

waves at delays shorter than 10 ms. Another promising alternative are multichannel discharge shock wave sources (Sect. 5.5.4).

Composite reflectors have been tested by different research groups (Loske and Prieto 1996; Bailey 1997b). Zhong and colleagues (1997b) designed a composite reflector for a laboratory electrohydraulic shock wave generator consisting of two brass ellipsoidal surfaces having the same distance between the two foci and different semi-major and semiminor axes. The spherical shock front produced at *F1* was partially reflected from one surface, and the remainder of the shock front was focused by the other section of the reflector. Both reflected shock waves converged towards *F2* with a delay of approximately 70 µs. As shown in Fig. 5.30, the inner reflecting surface was designed using three layers. The energy of the first and second shock wave could be varied by adding layers. When using the three layers, the shock wave was only reflected off the inner reflector. In that case the reflector had the same geometry as the reflector of a Dornier *HM3* lithotripter. The authors reported that no statistically significant difference could be detected between the in vitro stone fragmentation efficiency achieved using the *HM3* geometry and that obtained using two reflecting surfaces. A reason for this could be that the energy released at *F1* was divided into two when both reflecting surfaces were used.

Reflectors having two *F2* foci have also been tested experimentally (Prieto and Loske 1999). As shown in Fig. 5.31, two sectors of ellipsoidal reflectors with different focal distances were joined together to form a "bifocal" reflector. In contrast to standard lithotripter reflectors, the bifocal reflector was not rotationally symmetric. Shock waves generated at *F1* were divided into one part that converged towards *F2* and another part that was focused on *F2´*. The purpose of the design was to spatially and temporally phase out the shock waves produced by the electric discharges at *F1*. One sector of the bifocal reflector had the same geometry as an unmodified *HM3* reflector. The other part was designed so that the *F2* foci were separated 35 mm. Pressure records in the vicinity of *F2* and *F2´* showed a superposition of two shock

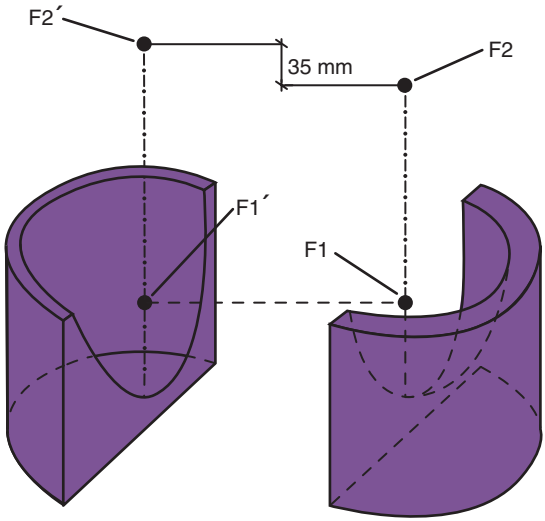


Fig. 5.31 Schematic of two ellipsoidal surfaces having different focal distances, before joining them together to form a bifocal reflector. Adapted from Prieto and Loske (1999)

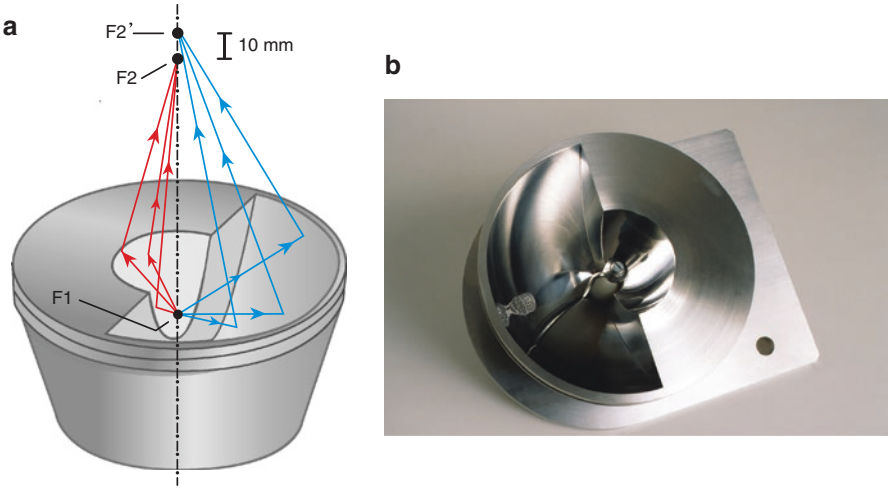


Fig. 5.32 (**a**) Schematic and (**b**) photograph of a research stainless steel bifocal reflector, designed to fit on a *Tripter Compact* (Direx Systems Corporation, Canton MA, USA) electrohydraulic lithotripter

waves. In vitro stone fragmentation and stone pitting was compared with that produced by an *HM3* reflector. Under certain circumstances, the shock waves reflected off the bifocal reflector were significantly more efficient in breaking standardized kidney stone phantoms than those reflected off the *HM3* reflector. It is believed that the novel reflector induced alternative compressions and rarefactions inside the stones, producing small fissures. Interestingly, enhanced stone fragmentation was not achieved at the region of maximum pressure, confirming that stone fragmentation does not only depend on the pressure amplitude.

Several years later, a specially designed bifocal reflector (Fig. 5.32) was tested on a *Tripter Compact* lithotripter (Direx Systems Corporation, Canton MA, USA)

and compared with the standard ellipsoidal reflector (Loske et al. 2004b). The *Tripter Compact* was selected because it was conceived so that changing from one reflector to another could be easily performed. The external dimensions of the bifocal reflector were the same as those of the standard reflector. One sector had a semimajor axis of 97.6 mm and a semiminor axis of 45.1 mm. The other sector had a 136.5-mm semimajor axis, and a 101.3-mm semiminor axis. The distance from the *F1* to the *F2* focus of the standard *Tripter Compact* reflector (178 mm) was equal to the distance from the *F1* foci to the middle between *F2* and *F2´* (Fig. 5.32a). In vitro stone phantom fragmentation showed that the bifocal reflector was more efficient in breaking stone phantoms than the standard reflector; however, only when the stones were surrounded by fluid (water). No difference in the fragmentation efficiencies for the standard and the bifocal reflector was observed when the stones were immersed in a tissue-mimicking jelly. In vivo tissue damage, observed after using the standard reflector was compared to that produced by the bifocal reflector. Macroscopic evaluation and histopathologic findings revealed that the bifocal reflector did not produce more tissue damage than the conventional reflector. Pressure measurements showed that two shock waves arrived at the dynamic focus with a delay of approximately 52 µs. It is interesting that this 52-µs-delay is between the 2–10 µs range recommended by Zhou and Zhong (2003) to suppress tissue injury and the 200–600 µs range used to intensify bubble collapse (Loske et al. 2002b, c). A main disadvantage of composite reflectors is that a different reflector is needed for each desired time delay between first and second shock wave.

In an attempt to reduce cavitation-induced damage to blood vessels, Zhong and Zhou (2001) adapted the reflector of a Dornier *HM3* lithotripter with a thin shell insert that covered most of the original reflector, except for a small part at the bottom (Fig. 5.33). The *F1* foci of the insert and of the original reflector coincided; however, their *F2* foci were located 5 mm apart. Because of this, the shock wave reflected off the ellipsoidal insert arrived approximately 4 µs before the shock wave reflected off the bottom of the *HM3* reflector. As a consequence, the trailing negative tensile component of the resulting pressure wave was partially canceled, preventing cavitation bubbles from expanding. Minimized tissue injury but no enhanced

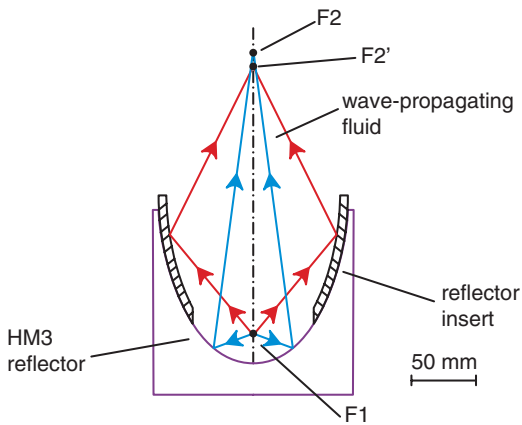


Fig. 5.33 Schematic of an *HM3* shock wave source implemented with a reflector insert. Adapted from Zhong and Zhou (2001)

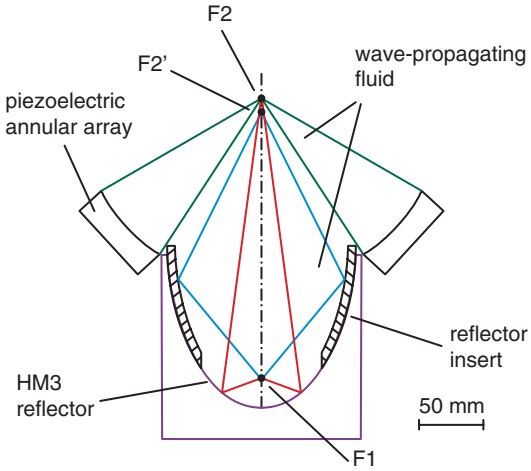


Fig. 5.34 Schematic diagram of an *HM3* shock wave source implemented with a reflector insert and a piezoelectric shock wave generator, consisting of six elements arranged around the reflector. Adapted from Zhou et al. (2004b)

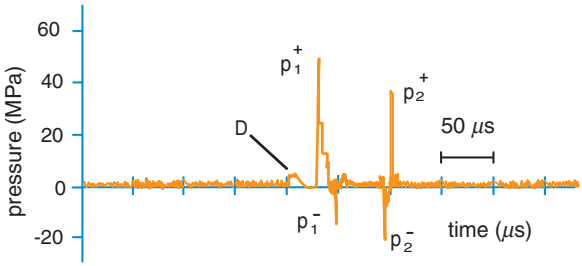


Fig. 5.35 Pressure waveform recorded with a PVDF needle hydrophone at the *F2* focus of a dual-phase reflector, showing the arrival of the direct, non-reflected shock wave (D), followed by a standard lithotripter shock wave and a phase-inverted pressure waveform

stone fragmentation was expected with this arrangement. As will be explained in Sect. 5.5.3, the same reflector insert was used a few years later in combination with a piezoelectric annular array (Fig. 5.34).

Tandem shock waves consisting of a standard lithotripter shock wave, followed by a phase-inverted wave (Fig. 5.35), have been tested on an experimental electrohydraulic lithotripter using a dual-phase reflector (Loske and Prieto 2001). This reflector was obtained by joining together two sectors of ellipsoids made out of different materials and having different major and minor axes (Fig. 5.36). One half of the reflector was made out of stainless steel and the other part was made out of polyurethane foam, which is a pressure-release material previously proposed by Bailey (1997a). The leading positive pulse, produced by reflection off the rigid part of the reflector, was supposed to compress previously existing microbubbles, and its negative phase to contribute to bubble growth. After certain delay, the negative pulse of the second pulse contributed to further bubble expansion. The inertia of this expansion seemed to be so strong that the compressive phase (p_2^+) following the second negative pulse could not reverse bubble expansion. Analysis of in vitro stone

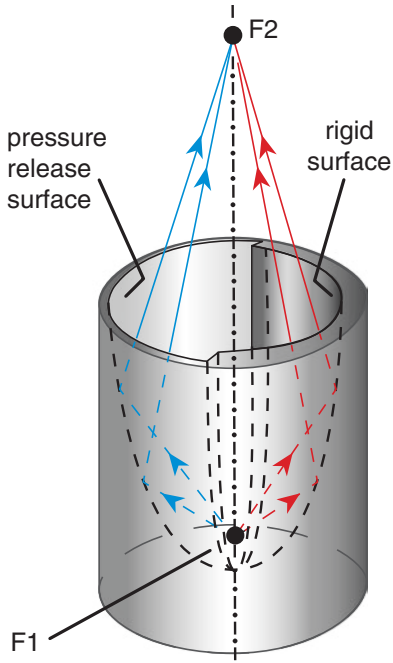


Fig. 5.36 Schematic of a dual-phase reflector obtained by joining together two sectors of ellipsoids made out of different materials, having different major and minor axes. One half of the reflector is made out of stainless steel and the other half is made out of a pressure-release material (polyurethane foam)

fragmentation and pitting of kidney stone phantoms revealed that, under certain circumstances, tandem shock waves consisting of two phase-inverted pulses were more efficient than conventional shock waves produced with an *HM3* reflector. In principle, it might be possible to improve the efficiency of this type of reflector by varying the length of the axes of one or both sectors; however, to find the ideal delay between pulses to enhance comminution of most urinary calculi would be a challenge. Furthermore, for a clinical application a more resistant material than polyurethane foam would be needed.

5.2.2 Dual Spark-Gap Shock Wave Sources

Bailey (1997a) was the first to investigate how the timing between two shock waves affects acoustic cavitation. He used a pair of confocal ellipsoidal reflectors, either both rigid or one rigid and one pressure-release, to study methods that influence cavitation. Different angles between the reflectors were also considered. A numerical model based on the Gilmore–Akulichev formulation and experimental results revealed that the second pulse may either reduce or increase bubble collapse energy depending on the time delay between pulses.

Other configurations of shock wave generators with two spark-gaps have also been tested. A patent describing a lithotripter with more than one shock wave source was registered by Faragalla et al. (2004).

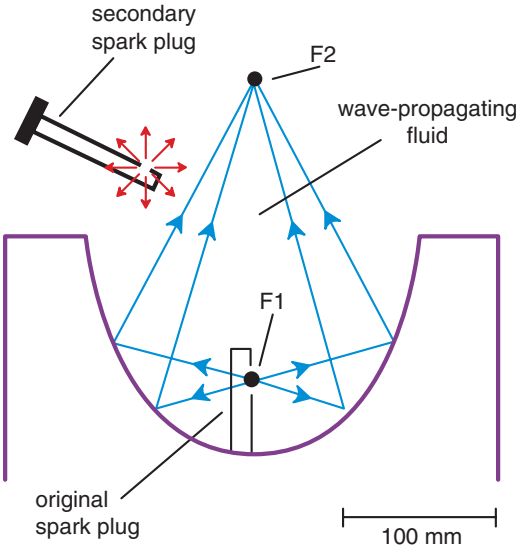


Fig. 5.37 Schematic of a research shock wave source with two electrodes, designed by Zhong et al. (1997b)

To demonstrate the advantages of controlled, forced collapse of cavitation bubbles to improve stone comminution during SWL, Zhong et al. (1997b) designed an experimental device with a second spark-plug placed close to the *F2* focus of a Dornier *XL1* lithotripter. The second spark-plug, located below *F2*, at an angle of 45° had no reflector surrounding it (Fig. 5.37). Its purpose was to produce a spherical shock wave that arrived at *F2* after the shock wave produced by the original *XL1* generator. Using high-speed photography the authors demonstrated that bubble collapse was asymmetric even without the presence of a solid boundary and that the resulting microjets are produced along the direction of the shock wave. A 400 μs-delay between the *XL1*-generated shock wave and the secondary shock wave directed the bubble collapse induced liquid jets towards the stone, enhancing in vitro fragmentation by 43 %. With this dual-spark system, tissue damage could be reduced, because fewer shock waves would be needed to pulverize a stone.

To generate simultaneous shock waves and confine cavitation, Sokolov and colleagues (2000, 2001, 2003) implemented a pair of opposing confocal electrohydraulic shock wave sources modeled after the Dornier *HM3* (Fig. 5.38). The simultaneous arrival of the two shock waves increased the pressure at the common *F2* focus. Enhanced cavitation could be observed by high-speed photography and demonstrated by analyzing damage to thin aluminum foils, placed at *F2* and aligned with the axis of symmetry of the two reflectors. Better in vitro fragmentation of kidney stone phantoms was also achieved. Bubble dynamics was recorded with a focused hydrophone and compared with a numerical analysis based on the Gilmore equation.

An electrohydraulic extracorporeal shock wave lithotripter with two identical confocal reflectors, one mounted under the treatment table and the second on a

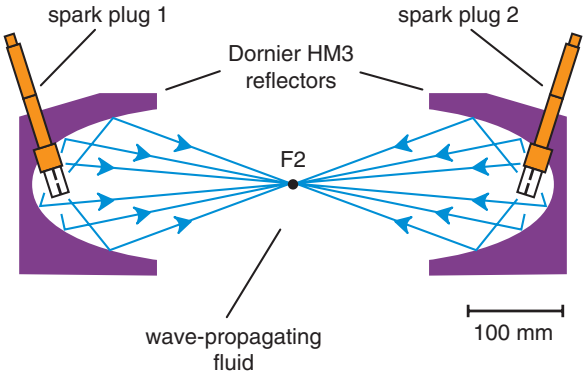


Fig. 5.38 Schematic of a research dual-pulse shock wave source consisting of two confocal shock wave generators. Adapted from Sokolov et al. (2001)

movable C-arm was developed and evaluated in vitro, in vivo, and on patients with renal and upper ureteric lithiasis (Sheir et al. 2001, 2003a, 2005). The best in vitro stone fragmentation results were obtained by adjusting the angle of the reflector axes at 90°. Compared with single pulse shock waves, synchronous dual-pulse shock waves induced less in vivo tissue damage to pig kidneys. Only minimal renal damage was observed even after 3000 twin pulses (6000 shock waves) generated at 14 kV. After randomizing 240 patients with a radio-opaque single renal stone to SWL either by a *Twinheads Lithotripter* (FMD, Lorton, VA, USA) or a *Lithotripter S* (Dornier MedTech GmbH, Wessling, Germany) Sheir and colleagues (2007) concluded that synchronous twin-pulse SWL has clinical advantages over standard SWL in terms of safety and efficacy.

Inspired by the potential benefits of a double spark-gap system, Direx Systems Corporation, the manufacturer of the first compact lithotripter (Fig. 5.39), developed the *Duet* lithotripter (Fig. 5.40), with two confocal electrohydraulic shock wave sources at an angle of approximately 76° to each other. The lithotripter could be operated on simultaneous, alternating, or single-pulse mode. Initial in vitro experiments were encouraging and showed that simultaneous and alternating modes are more efficient to fracture kidney stone phantoms than single-pulse shock waves (Greenstein et al. 2004). Handa et al. (2007) studied the acute effects on the renal function and morphology in the pig and concluded that a clinical dose of shock waves delivered in the synchronous mode produces a renal response similar to that obtained with a clinical dose from an *HM3* lithotripter. In another in vivo experiment to test the *Duet* lithotripter, Handa and colleagues (2009b) reported that a clinical dose of shock waves delivered in the alternating mode only produced minimal alteration in the renal function and a small hemorrhagic lesion. According to their results, delivery of shock waves from two sources was not inherently dangerous and firing the two sources at a combined rate of 240 shock waves per minute did not cause significant morphological injury to the kidney. The lesion produced by 2400 shock waves (1200 shock waves per shock wave source) at 2 Hz in the alternating mode at a power level of 10 was approximately one fifth of the functional renal volume (FRV) observed after 2400 shock waves delivered with a Dornier

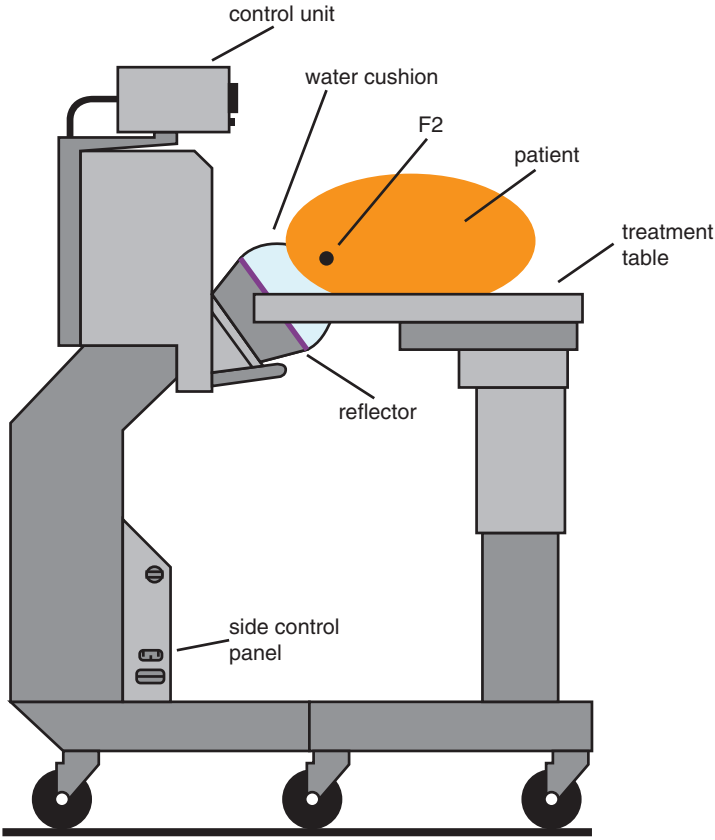


Fig. 5.39 Schematic of a *Tripter Compact* electrohydraulic extracorporeal shock wave lithotripter (Direx Systems Corporation, Canton MA, USA). A C-arm fluoroscopy unit, not shown here, was easily coupled to the system

HM3 at the same shock wave rate and a discharge voltage of 24 kV (Handa et al. 2007). These were encouraging results even if the FRV could not be compared directly, because treatment conditions were not the same. Direx still manufactures dual-shock wave source lithotripters; however, the new model (*Duet Magna*) uses electromagnetic instead of electrohydraulic shock wave sources (Sect. 5.3.3).

5.3 Electromagnetic Lithotripters

The physical principle to generate shock waves with an electromagnetic transducer, also referred to as electromagnetic shock wave emitter (EMSE), was published in 1962 by Eisenmenger. Electromagnetic shock wave generators for SWL were developed in the early 1980s (Wilbert et al. 1987). Nowadays, four different designs

Fig. 5.40 Photograph of a *Duet* lithotripter (Direx Systems Corporation, Canton MA, USA), showing the two confocal electrohydraulic shock wave sources with their elastic membranes covering the reflectors before filling them with water

of electromagnetic shock wave sources are available for clinical use: flat coil, cylindrical coil, conical coil, and self-focusing systems. The pressure waves generated by electromagnetic lithotripters are high intensity ultrasonic waves. At high energy settings, these waves transform into shock waves as they propagate towards the focus of the lithotripter. This occurs because of the nonlinear distortion produced by focusing. An advantage of electromagnetic sources is that shock wave generation is highly reproducible. The pulse-to-pulse variability of flat coil systems is about 2 % (Coleman and Saunders 1989). Other advantages are the wide range of energy that can be used as well as the long lifetime of the shock wave source (more than a million shock waves). Electromagnetic shock wave sources produce much less noise than electrohydraulic lithotripters. In a prospective study Tuncer et al. (2014) evaluated the effects of SWL on the hearing status of patients treated on an electromagnetic *Compact Sigma* lithotripter (Dornier MedTech GmbH) and concluded that SWL with this device does not cause harmful effects on the hearing function.

5.3.1 Flat Coil Shock Wave Sources

In flat coil lithotripters, a strong pulsed current is sent through a circular copper coil, which is opposite to a conductive metallic membrane, separated by a thin insulating layer. The high-voltage discharge (16–22 kV) applied to the coil induces a rapidly changing magnetic field and Eddy currents in the metallic membrane, resulting in

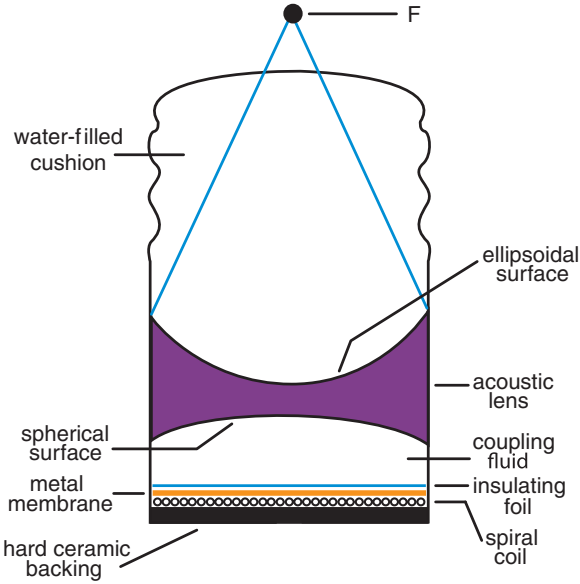


Fig. 5.41 Schematic of a flat coil electromagnetic shock wave source

an explosion-like deflection of the membrane. The physical principle is analogous to that of a loudspeaker. Some designs use a secondary coil to generate the vibrations of the diaphragm. The sudden movement of the membrane produces pressure waves in a wave-propagating fluid (e.g., degassed water). The pressure waveform depends on the generated current pulse and the properties of the solenoid and the membrane. The plain pressure waves are focused by a polystyrene acoustic lens (Fig. 5.41) with a biconcave shape. Proximal to the vibrating membrane the lens has a spherical surface and distal to the membrane the surface is ellipsoidal. A shock wave with a rise time of approximately 100 ns, a relatively small focal zone and a peak-positive pressure $p+$ of up to 100 MPa is produced at the focal spot. The rise time of the positive pressure pulse produced with this system is longer than for electrohydraulic lithotripters (Coptcoat et al. 1987), and the waveform includes a trailing positive pressure oscillation (Fig. 5.42) (Bailey et al. 2006). As in other shock wave sources described in this chapter, a water-filled silicone cushion is used to couple the shock waves into the patient. Water is degassed and deionized. Other wave-propagating fluids may also be used. The basic electrical circuit is similar to that of electrohydraulic shock wave sources. An advantage of electromagnetic sources is that they are highly reproducible from pulse to pulse; however, according to Mishriki 1994, during its lifetime, the maximum peak-positive pressure pulse of an electromagnetic shock wave source may fall off by as much as 50 %. Plane electromagnetic shock wave sources are relatively small allowing their integration into multifunctional treatment systems. Nowadays, electromagnetic shock wave sources are the most commonly used for SWL.

A pioneer in the design of electromagnetic shock wave sources for clinical applications was Siemens Healthcare GmbH in collaboration with the University of Mainz,

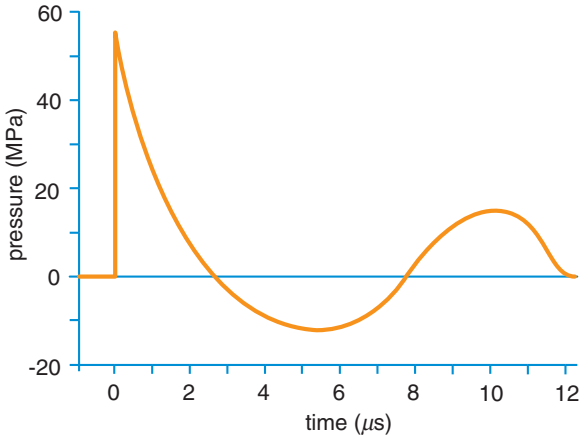


Fig. 5.42 Typical pressure profile recorded at the focus of a flat coil electromagnetic extracorporeal shock wave lithotripter, revealing the presence of a relatively strong secondary compressive wave with a peak amplitude approximately 10 μs after arrival of the leading shock wave

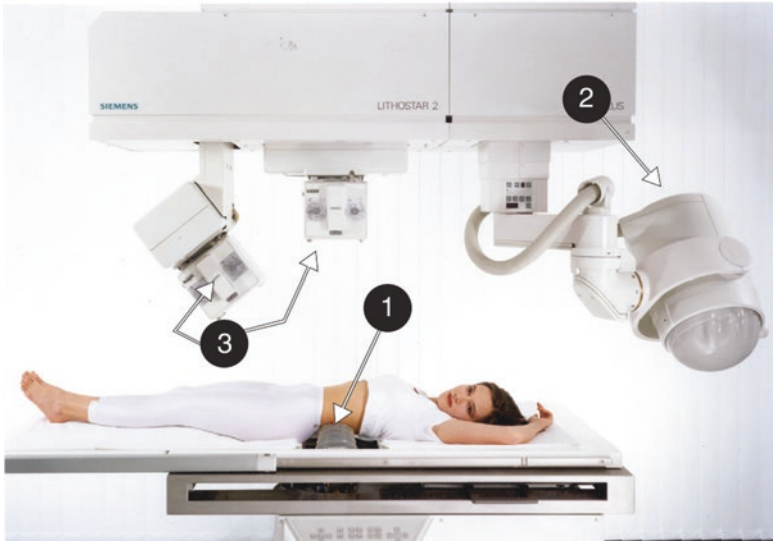


Fig. 5.43 Photograph of the *Lithostar 2 Plus* lithotripter with three electromagnetic shock wave sources, showing (*1*) the left undertable shock wave source, (*2*) the overhead shock wave source with in-line ultrasound scanner, and (*3*) the X-ray sources. (Courtesy of Siemens Healthcare GmbH, Erlangen, Germany)

Germany. The first Siemens lithotripter (*Lithostar*) with biplane X-ray systems and two electromagnetic shock wave sources was on the market for many years (Mobley et al. 1993). In the second model (*Lithostar 2 Plus*), the diameter of the lenses was enlarged, their focal depth was increased from 113 to 120 mm, and the dimensions of their focal zones were reduced (Vandeursen et al. 1993; Loske 2007). Therefore the energy was distributed over a larger skin area and concentrated onto a smaller volume at the stone. This change increased the maximal EFD from 0.24 to 0.60 mJ/mm^2. The *Lithostar 2 Plus* (Fig. 5.43) was also available with a shock wave head with

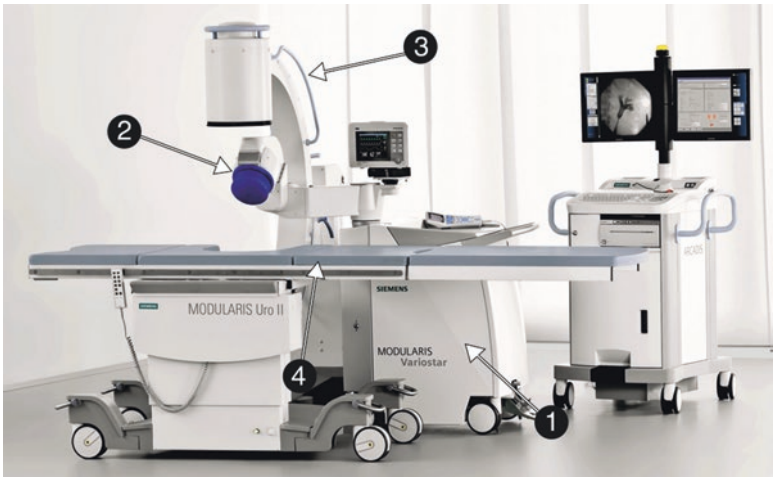


Fig. 5.44 Photograph of the *Modularis Variostar* mobile therapy unit (*1*) with its electromagnetic shock wave source (*2*), coupled to an *Arcadis* multi-purpose mobile C-arm (*3*), and a *Modularis Uro* endourology table (*4*). (Courtesy of Siemens Healthcare GmbH, Erlangen, Germany)

integrated ultrasound installed on an overhead module to complement the two undertable shock wave heads, facilitating SWL of urinary, pancreatic, and gallbladder stones, as well as bile duct stones (Rawat et al. 1990). At maximum generator voltage (level 9), the p^+ value measured with a PVDF hydrophone (Imotec GmbH, Würselen, Germany) at the focus of the overhead module was approximately 64 MPa. This was twice the peak-positive pressure registered at the focal point of the undertable shock wave sources at their maximum generator voltage (19 kV) (Vergunst et al. 1989).

A more recent flat coil electromagnetic lithotripter is the *Modularis Variostar* (Siemens Healthcare GmbH). It is a mobile device with an endoscopic treatment table, integrated fluoroscopic guidance and a shock wave source with a focal distance of 140 mm and an aperture angle of 48° (Fig. 5.44). The shock wave unit can be fixed at different angles and used in the undertable therapy position for the treatment of kidney stones and in the over-table position to treat ureter, bladder, and bile duct stones, with the patient in supine position at all times. Ultrasound and X-ray localization is available. Laser-guided alignment facilitates the adjustment of the shock wave unit, the treatment table, and the C-arm. The total energy delivered to the patient is registered and shown at the end of each session. According to data obtained by the manufacturer using a light spot hydrophone (LSHD), developed by Siemens and the University Hospital Erlangen, Germany (Granz et al. 2004), the peak-positive (p^+) focal pressure goes from approximately 11 MPa for the lowest energy setting to approximately 59 MPa for the highest setting. The maximum energy equals 113 mJ. Hassouna and colleagues (2011) treated more than thousand patients with renal or ureteric stones using the *Modularis Variostar*. Their study revealed a high success rate and an overall efficiency quotient (EQ) (Sect. 5.6.12) of 0.66. This lithotripter is considered as a very effective tool for treating urinary calculi, especially smaller than 20 mm in diameter and may also be used for ESWT.

Improvements to flat coil electromagnetic shock wave sources, such as tandem shock wave emission and modification to the acoustic lens, have been proposed to enhance cavitation at the focal zone. Pierre et al. (2008) adapted a Siemens *Modularis-Litho* shock wave generator to produce a shock wave generated at a discharge voltage of 12.5 kV, followed about one millisecond later by a second wave generated at 17 kV. In vitro stone fragmentation efficiency, defined as the percentage of fragments smaller than 2 mm, improved using 750 tandem shock waves; however, the difference was not statistically significant at a lower dose.

As mentioned before, a characteristic of the pressure waveform generated by electromagnetic shock wave sources is the emission of a secondary compressive wave (Fig. 5.42). This pulse is a result of the current oscillation in the coil and has less amplitude than the leading shock wave; however, its amplitude is sufficient to suppress the cavitation bubbles induced by the main shock wave. Since, as explained in Sect. 4.7, cavitation is a main fragmentation mechanism during SWL, the second compressive pulse reduces the fragmentation efficiency of electromagnetic devices. To overcome this issue, a modified lens has been proposed (Zhong et al. 2011; Mancini et al. 2013; Neisius et al. 2014). The novel lens has an annular groove on the surface proximal to the membrane, i.e., on the spherical surface of the lens (Fig. 5.45). The groove produces a pressure pulse that arrives at the focal spot shortly after the leading shock wave generated by the main part of the lens. This occurs because the propagation velocity through the groove is lower. The resulting shock wave does not have the non-desired second compressive wave, because it is eliminated by pulse superposition as the pressure waves exit the lens and converge towards the common focal spot. To compensate for the energy loss caused by the destructive wave superposition, the voltage of the shock wave source must be increased a few kilovolts. Since increasing the voltage shifts the spot of highest peak-positive pressure towards the shock wave source, the geometrical focus of the

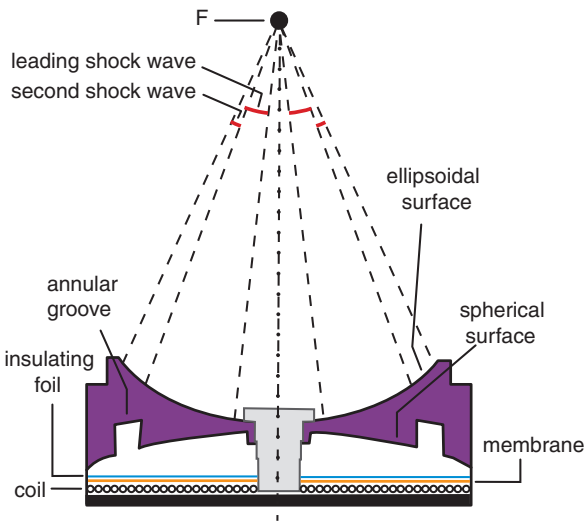


Fig. 5.45 Schematic diagram of a novel lens designed to improve stone comminution during SWL. (Adapted from Neisius et al. 2014)

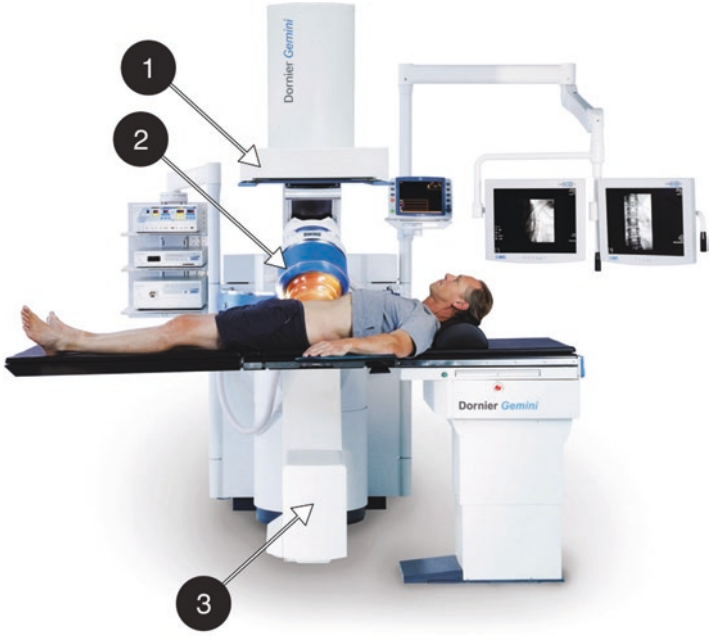


Fig. 5.46 Photograph of the Dornier *Gemini* electromagnetic shock wave lithotripter and urological workstation, showing (*1*) the flat panel detector, (*2*) the shock wave source, and (*3*) the X-ray source. (Courtesy of Dornier MedTech GmbH, Wessling, Germany)

new lens was set several millimeters upwards from the original focus. As a result of this modification, the acoustic focus of the new lens gets close to the stone at high output voltages, improving the fragmentation efficiency while reducing tissue trauma risk without altering the main design of the lithotripter. Thorough in vitro and in vivo studies implementing the new lens on a Siemens *Modularis* shock wave head demonstrated improved stone comminution and minimal tissue damage (Mancini et al. 2013; Neisius et al. 2014). Pressure measurements revealed that the new lens generated a pressure profile similar to that of the Dornier *HM3*.

The *Gemini* (Dornier MedTech GmbH) is another representative last-generation electromagnetic shock wave lithotripter (Fig. 5.46). Variable position of the two monitors, access to the patient from all sides, orbital movement of the C-arm and the design of the treatment table allows not only SWL and URS, but also percutaneous nephrolithotomy (PCNL). Switching from SWL to endourological procedures without moving the patient is possible. A load capacity of up to 250 kg and a maximum penetration depth of 170 mm are suitable for the treatment of obese patients. Continuous stone tracking during X-ray C-arm rotation with unobstructed stone visualization is possible. Since the shock wave source can be rotated around the patient, he or she may remain in a comfortable supine position for any stone location. The operator can mark the stone to be treated at both AP (anteroposterior) and CC (craniocaudal) projection X-ray images. Then, the patient is moved automatically to align the stone with the

lithotripter focal spot. Isocentric ultrasound and real-time monitoring of the stone is another feature of the device. The manufacturer offers either a large image intensifier or a flat panel detector with a large field of view and three electromagnetic shock wave sources. The *220f XXP*, the *220f XXP HP*, and the *140f FarSight* shock wave generator has a maximum EFD of 1.9, 1.6, and 0.86 mJ/mm^2, respectively and a maximum E_{12mm} (Sect. 3.5) of 110, 110, and 62 mJ, respectively. According to the manufacturer, p^+ can be varied from 49 to 90 MPa with the *220f XXP*, from 49 to 77 MPa with the *220f XXP HP*, and from 9 to 53 MPa with the *140f FarSight*. All pressure measurements were performed using an FOPH (RP Acoustics), according to the IEC standard. A video camera for monitoring the coupling membrane from the inside of the shock wave source is also offered and, as will be mentioned in Sect. 5.6.8, may be crucial to assure a bubble-free shock wave path into the patient.

5.3.2 *Cylindrical Coil Shock Wave Sources*

As mentioned in Chap. 2, an electromagnetic shock wave source that does not use an acoustic lens was developed and patented by Storz Medical AG, Tägerwilen, Switzerland (Wess et al. 1990; Köhrmann et al. 1995; Wess 2012). As shown in Fig. 5.47, a cylindrical coil and a metallic membrane are arranged inside a water-filled parabolic metallic reflector. The membrane is suddenly accelerated radially away from the coil by induction of a magnetic field. The design works analogous to the plain coil shock wave source; however, in this case the acoustic pulses emerge radially, perpendicular to the beam axis. The cylindrical pressure wave is focused concentrically onto the focus *F* of the shock wave source after reflection off the paraboloidal reflector and, depending on the energy setting, may steepen into a

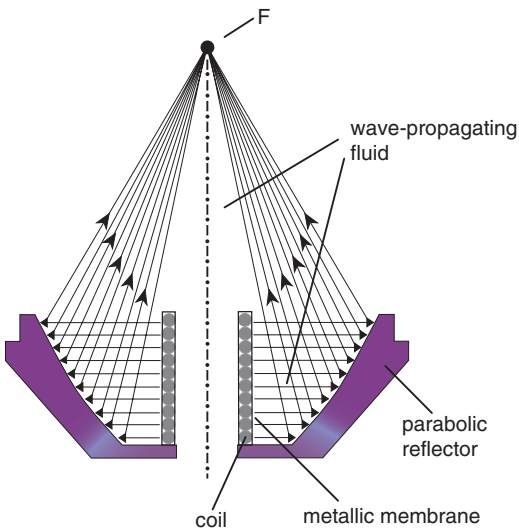


Fig. 5.47 Schematic diagram of the cylindrical coil shock wave generator developed by Storz Medical AG in Tägerwilen, Switzerland

shock wave. A main advantage of the cylindrical source is the possibility to incorporate an in-line ultrasound scanner or in-line X-ray localization into the hollow cylinder without reducing the shock wave energy. It also allows the design of systems with large apertures and focal depths, and provides a broad range of energy settings. A shock wave source with variable focal size was also developed (Häcker et al. 2005; Leistner et al. 2007; Häcker and Wess 2010).

Choi et al. (2011) investigated the influence of the thickness of both the metallic and the insulating membranes surrounding the solenoid of a cylindrical electromagnetic shock wave generator. According to their results, shock wave production was maximized when the membranes had the smallest tested thickness (50 µm).

A modern example of this type of lithotripter is the Storz *Modulith SLX-F2 connect*, a urological workstation with the feature that the operator can select between two focal sizes even during treatment (Fig. 5.48). Focal size variation is achieved by varying the pulse duration. The large focal zone (50 mm × 9 mm) is adapted to treat renal stones, whereas the small focus (28 mm × 6 mm) is recommended for ureteral stones. The energy E_{12mm} can be varied between 11 and 154 mJ. In the small focus modality, a peak-positive pressure between 5 and 150 MPa is available and in the extended focus modality p^+ can be adjusted between 5 and 90 MPa. All pressure measurements were performed by the manufacturer using a fiber-optic hydrophone

Fig. 5.48 Photograph of the *Modulith SLX-F2 connect* electromagnetic extracorporeal shock wave lithotripter and urological workstation, showing (*1*) the shock wave source with in-line ultrasound, (*2*) the X-ray source, and (*3*) the dynamic X-ray (430 × 430 mm) flat panel detector. (Courtesy of Storz Medical AG, Tägerwilen, Switzerland)

according to the standard 61846 of the IEC. The energy density at the patient's skin is relatively low because of the large aperture of the shock wave source (300 mm), minimizing the need for analgesics. The left or right kidney can be treated without repositioning the patient. It is the urologist's choice whether to use the small or the large focal zone. Since kidney stones may be bigger and have a tendency to move, a recommendation is to treat them with the large focal-zone setting, reducing the peak pressure in the kidney. Hard and impacted ureter stones may be broken with higher peak pressures without causing lesions to the ureter. Additional features of the *Modulith SLX-F2 connect* are integrated X-ray and ultrasound imaging and an automatic system to easily position the stone by tapping the image of the stone on the touch screen. An advantage of the cylindrical shock wave source is that shock waves and in-line ultrasound follow the same path through the tissue. The ultrasound transducer shows obstacles, such as ribs or gas-filled organs. Simultaneous X-ray and ultrasound imaging is also possible. Obese patients of up to 225 kg can be treated using an optional therapy source with a focal depth of 180 mm. An integrated patient foil allows for comfortable, safe, and stable patient support and is favorable for the treatment of small children without further modifications to the treatment table. In a study published by Elkoushy et al. (2011), the *Modulith SLX-F2* lithotripter had an EQ of 0.66 (Sect. 5.6.12). De Sio et al. (2007) published a study that included 233 SWL-treated patients with symptomatic solitary renal or ureteric stones. The success rate after one session was approximately 84 % and 83 % for renal and ureteric stones, respectively, and the overall EQ was 0.64. More clinical results obtained with this lithotripter can be found in the literature (Tiselius 2008; Zehnder et al. 2011; Razvi et al. 2012).

Recently, Wang and Zhou (2016) reported the results of tests performed with the modified reflector of a cylindrical coil shock wave generator manufactured by ANK Medical Equipment (Shenzhen, China). As shown in Fig. 5.49, the standard parabolic reflector was divided into four parts. Each segment could be shifted away from the coil, maintaining the same axis of symmetry. A numerical model and pressure measurements demonstrated that the focal zone of the shock wave source was widened by moving the sectors away from the coil. Lower p^+ and p^- values were recorded with the novel design. Compared with the location of maximum negative pressure in the original design, the spot in the pressure field where the p^- was recorded appeared closer to the focus, i.e., it moved from a pre-focal spot towards the geometrical focus. The shock wave-induced stress inside the stone was evaluated implementing a finite difference time-domain program based on the elastodynamic equations of Newton's second law and Hooke's law. Furthermore, the dynamics of a 3 μm bubble was described by the Gilmore formulation (Church 1989) and solved using the fifth-order Runge–Kutta–Fehlberg method with a step-size control algorithm (Zhu and Zhong 1999). Good agreement between the numerical simulation and the experimental results was reported in both pressure waveform and pressure distributions along and transverse to the beam axis. In vitro stone fragmentation tests were performed with spherical stone phantoms (diameter 10 mm) made of plaster-of-Paris. Vinyl tape-covered aluminum foil was exposed to shock waves inside the conventional and novel arrangement to analyze pitting and

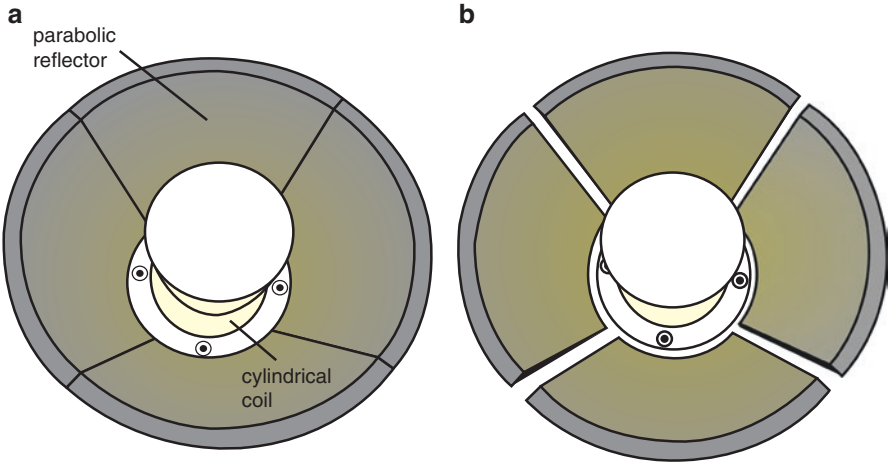


Fig. 5.49 Sketch of the modified cylindrical coil shock wave generator proposed by Wang and Zhou (2016) to broaden the focal zone, vary the ratio of the peak-positive to peak-negative pressure, and shift the location of the peak-negative pressure towards the geometrical focus. (**a**) Shows the four segments forming a standard parabolic reflector and (**b**) shows the shifted segments

denting damages caused by acoustic cavitation. Foils were exposed to 100 shock waves at a rate of 1 Hz. The greatest amount of cavitation activity occurred in a region 10–30 mm proximal to the geometrical focus. As a result of moving the sectors away from the axis of symmetry, stone fragmentation efficiency enhanced up to 1.8 fold. An advantage of the design is that the ratio of compressive to tensile pressure may be adjusted by shifting the reflector sectors.

5.3.3 Conical Coil Shock Wave Sources

A relatively new design is the conical coil electromagnetic shock wave generator. Similar to the system described in the previous section, the coil is arranged inside a metallic reflector; however, in this case the coil is not cylindrical and the reflector is a modified parabolic reflector. With this concept, shock wave sources with a relative small aperture and a large focal zone can be designed. A lithotripter with two confocal conical electromagnetic shock wave sources as the one shown in Fig. 5.50, located at 36° between each other, is the *Duet Magna* (Direx Systems Corporation), released in 2010. It is equipped with an in-line ultrasound scanner located inside each shock wave source and has a modular compact design (Fig. 5.51). Ultrasound real-time imaging during the whole treatment as well as simultaneous X-ray and ultrasound imaging is possible. Fluoroscopy units from a variety of manufacturers can be coupled to the system. An advantage of operating this lithotripter in the simultaneous mode is that the −6 dB focal zone is no longer cigar shaped, but can be considered as having the shape resulting by the superposition of two cigar shaped volumes.

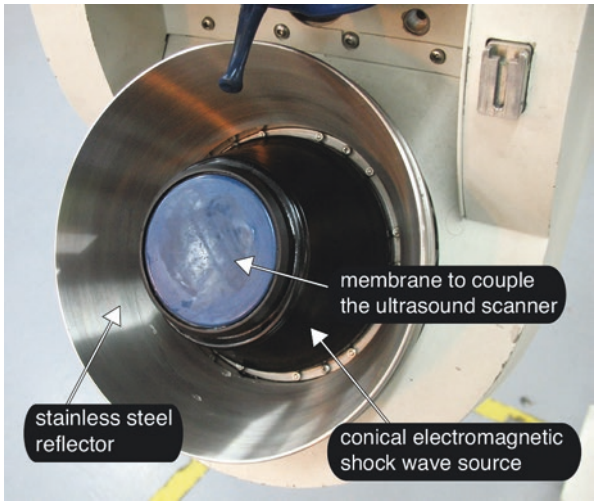


Fig. 5.50 Photograph of one of the two conical coil shock wave generators of a *Duet Magna* lithotripter without the latex membrane that covers the shock wave source. (Courtesy of Direx Systems Corporation, Canton MA, USA)

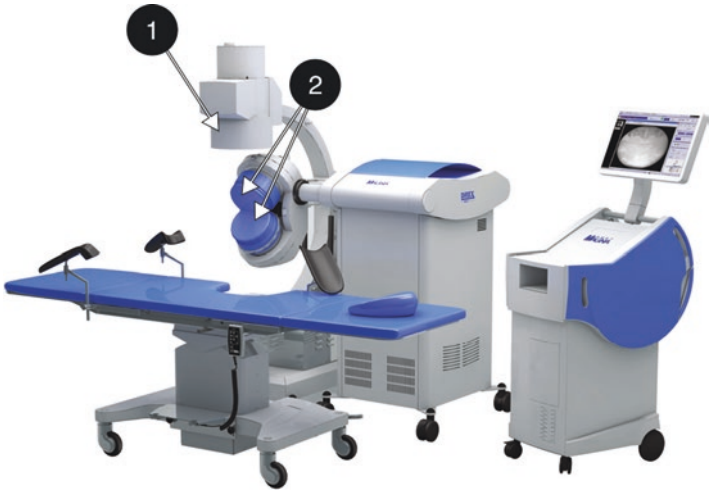


Fig. 5.51 Photograph of a *Duet Magna* extracorporeal lithotripter, showing (*1*) the X-ray image intensifier and (*2*) the two confocal electromagnetic shock wave sources (Courtesy of Direx Systems Corporation, Canton MA, USA)

A focal volume having this shape is closer to the ideal focus (Fig. 3.7) and is expected to produce less tissue damage, because less tissue is exposed to high shock wave energy. To obtain a symmetric focal volume, both shock wave sources are equal. An image of the resulting pressure distribution in the vicinity of the focal spot is shown in Fig. 5.52. Compared to a cylindrical coil of the same height, a cone-shaped coil has a larger pressure-pulse-emitting area and the aperture of the shock wave source can be reduced. The aperture of the *Duet Magna* shock wave sources is 220 mm.

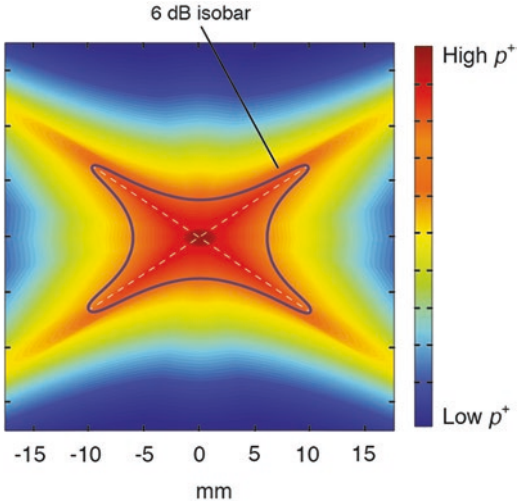


Fig. 5.52 Bi-dimensional image of the pressure distribution generated in the vicinity of the focal spot of a *Duet Magna* lithotripter, after simultaneously firing its two electromagnetic shock wave sources. The colors (*eBook*) represent positive peak pressure variations, according to the vertical chart at the right side of the figure. The pressure at each point inside the region bordered by the 6 dB isobar equals to 50 % or more of the maximum peak-positive pressure. (Courtesy of Direx Systems Corporation, Canton MA, USA)

An additional feature of this dual-head lithotripter is that the software alerts the user when a replacement of one of the two electromagnetic transducers is required. As in all dual-head lithotripters, assuring good coupling of both water cushions is crucial and requires expertise. Conical coil shock wave sources are not exclusive of dual-head lithotripters. A single conical coil shock wave generator is used in the Direx *Integra* lithotripter.

5.3.4 Self-Focusing Shock Wave Sources

The working mechanism of the self-focusing electromagnetic shock wave source, developed at the University of Stuttgart, Germany, is analogous to that of flat coil systems. A spiral coil arranged on a spherical concave surface repels a copper diaphragm mounted above to the coil (Fig. 5.53). The sudden movement of the membrane produces a pressure wave that converges towards the center (*F*) of the arrangement and steepens into a shock wave in the vicinity of *F* (Staudenraus 1991; Eisenmenger et al. 2002). The system produces a large focal volume and relatively low pressure. As in other extracorporeal shock wave sources, shock wave coupling into the body is facilitated via a water-filled cushion. Reduced pain and tissue trauma are considered as advantages of this design. The big focal volume provides a large error margin in stone targeting. Encouraging clinical results were reported after using the first version of the self-focusing electromagnetic lithotripter, developed jointly by

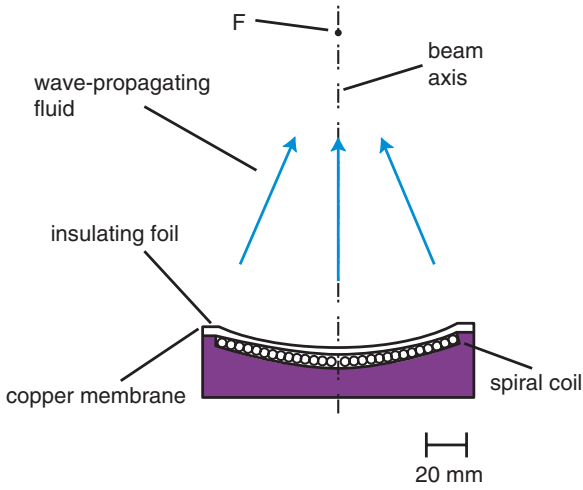


Fig. 5.53 Schematic of a self-focusing electromagnetic shock wave source

the University of Stuttgart and the Suzhou XiXin Medical Instruments Co. Ltd, Wuxian-Suzhou, China. The shock wave source was integrated into a compact lithotripter in an over-table arrangement. An ultrasound probe was mounted on the generator housing and could be moved around the generator axis (Loske 2007). The system produced low tensile pressure (about −5 MPa) and little pain, because the energy was dispersed over a large area at the skin. Its large focal volume is considered to enhance stone comminution by circumferential compression (Sect. 4.8). Good clinical outcomes were achieved with low pressure and a relatively small number of shock waves (Eisenmenger et al. 2002). The low shock wave rate used during these treatments might have contributed to enhance SWL outcomes (Sect. 5.6.5).

Nowadays, Suzhou XiXin Medical Instruments offers the *CS-2012A-3* mobile lithotripter with a 10^6-shot lifetime coil that was approved by the FDA in September 2014 (Rassweiler et al. 2014). So far, approximately 200 flat coil lithotripters are operating in China. The lithotripter has a focal distance of 145 mm and can be easily coupled with most currently used C-arms and ultrasound systems. The length of the focal volume along the beam axis is approximately 95 mm with a diameter of about 10 mm. For generator voltages between 7.0 and 10.5 kV, the peak-positive and peak-negative pressure values range from approximately 8 to 40 MPa and −3 to −4 MPa, respectively. These measurements were obtained by the manufacturer according to the IEC 61846 standard.

5.4 Piezoelectric Lithotripters

In 1880 the brothers Pierre and Jacques Curie demonstrated that application of mechanical stress to certain materials produces electricity, a phenomenon known as *piezoelectric effect*. Little later, Gabriel Lippmann mathematically deduced the *converse piezoelectric effect*, i.e., the conversion of a high-voltage peak into

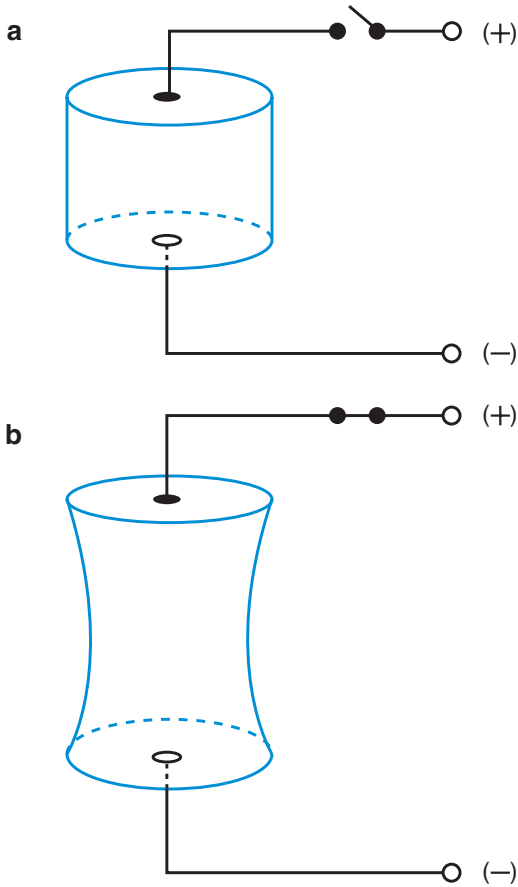


Fig. 5.54 Sketch of a piezoelectric element (**a**) before and (**b**) after applying an electrical field. The increase in height has been exaggerated. A piezoelectric crystal as used in biomedical applications changes about 0.1 % of its height when an external electric field is applied

mechanical strain, which is used to produce pressure pulses for several biomedical applications. Both phenomena play an important role in many areas of research and industry, such as non-destructive testing, sonar locating and ranging, production of sensors, focusing of optical assemblies, construction of atomic force microscopes, microbalances, and piezoelectric motors. Common piezo-ceramics are barium titanate and lead-zirconate titanate. An important advantage of these materials is their long lifespan. Polycrystalline piezoelectric ceramic elements suddenly change their size a few micrometers when an electrical pulse is applied to them (Fig. 5.54). When these elements are in contact with a fluid, their fast expansion produces a pressure pulse, followed by a tensile phase. Depending on the design of the shock wave source, tenths to thousands of these elements are arranged on a surface. The generated pressure waveform depends on several factors, such as the insulating material at the front of the transducer, the backing material on its rear side, the shape of the piezoelectric elements, and the electrical excitation pulse (Dreyer et al. 2000).

5.4.1 *Self-Focusing Shock Wave Sources*

As mentioned in Chap. 2, piezoelectric shock wave sources were initially developed in Germany between 1978 and 1985 by the company Richard Wolf GmbH in Knittlingen, the University of Saarland, and the University of Karlsruhe. These transducers produce pressure waves by a high-voltage discharge of approximately 5–10 kV applied across a mosaic pattern of piezoelectric elements mounted on the inner surface of a spherical concave aluminum backing (Fig. 5.55). In most devices, the arrangement is placed inside a fluid-filled cavity, sealed with a thin membrane that comes into contact with the skin of the patient. Each piezo-ceramic element expands a few micrometers, generating a pressure pulse that propagates towards the center (F) of the arrangement. Superposition of all pressure pulses and nonlinear effects produce a shock wave in the vicinity of F. If a spherical arrangement is used, the system is self-focusing and does not require lenses or reflectors. A spark-gap trigger switch or a high-voltage thyristor, driven by a pulse generator, is used to control the discharge rate of the shock waves. Similar to electrohydraulic systems, the electric circuit of piezoelectric shock wave sources mainly consists of a capacitor charging unit and a discharge control system. Piezoelectric sources depend on nonlinear acoustic propagation to generate shock waves in the neighborhood of the focal spot. Main advantages of piezoelectric shock wave sources for SWL are their long lifespan (more than a million shock waves) and less need for analgesia due to the excellent focusing capabilities of the transducer. Moreover, there is no need for ECG-triggering, because the electromagnetic radiation to the patient is low. An additional advantage of piezoelectric shock wave sources, not only for SWL, is the possibility of modifying the pressure wave by altering the excitation of the piezo-ceramic elements. Their high reproducibility is convenient for research purposes (Chap. 7) and to evaluate the emitted pressure field. Contrary to measurements with electrohydraulic shock wave sources, no averaging of pressure records is needed.

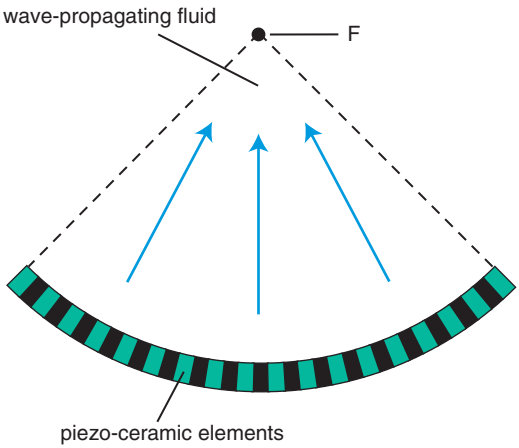


Fig. 5.55 Schematic of a single-layer piezoelectric shock wave source

In the early days of SWL, the most popular piezoelectric lithotripter and a competitor for the Dornier *HM3* was the *Piezolith 2300* (Richard Wolf, GmbH, Knittlingen, Germany). It appeared on the market in 1986 (Fig. 2.11). Its piezoelectric shock wave generator with 3400 piezo-ceramic crystals (length 5 mm, diameter 6 mm) mounted on a self-focusing concave bowl-shaped aluminum backing (radius approximately 350 mm) with large aperture (approximately 500 mm) and embedded in epoxy resin, produced low energy density at the patient's skin and high EFD at the focus. Due to its small focal zone, tissue damage could be reduced; however, precise targeting was essential to obtain good results. Small focal volumes are also convenient to treat stones in the pancreas, common bile duct, and salivary gland. A significant advantage of this mobile unit compared to the *HM3* was its small water bath. Piezoelectric open water bath lithotripters have also been suitable as research devices (Fernández et al. 2009a, b, 2013). A comparison between the predecessor of the *Piezolith 2300*, the *Piezolith 2200,* and the modified *HM3* revealed that the rate of successful disintegration and number of auxiliary measures were similar with both lithotripters; however, many patients treated with the *Piezolith 2200* required more than one SWL session (Rassweiler et al. 1987, 1989). An advantage of the piezoelectric system was that almost all treatments were performed without anesthesia, whereas with the *HM3*, analgesia was needed in most patients. Good treatment outcomes with the piezoelectric lithotripter were also reported by other authors (McNicholas et al. 1989; Ruoppolo et al. 1989; Tombolini et al. 1989). Popular competitors of the *Piezolith* models were the *LT01* and *LT02* piezoelectric lithotripters (Fig. 2.12), manufactured by the French company EDAP Technomed (Vallancien et al. 1988; Miller et al. 1989; Ryan et al. 1991; Tan et al. 1991; Wang et al. 1993; Anderson et al. 1995; Kim and Moon 1997; Lee et al. 2005). The first piezoelectric shock wave lithotripter with in situ X-ray and ultrasound location manufactured by Richard Wolf GmbH, the *Piezolith 2500*, was available in 1990. This model was replaced by the *Piezolith 2501* in which the location units could be used separately for diagnosis. The large size of most piezoelectric shock wave sources was considered a disadvantage, mainly because they were not suitable for integration into multifunctional systems. As explained later in this section, this was efficiently resolved by Richard Wolf GmbH using a dual-layer shock wave source (*Piezolith 3000*).

An additional advantage of piezoelectric shock wave sources, especially those with arrays of piezoelectric elements that are driven by individual impulse generators, is the possibility to emit specifically designed acoustic pressure fields (Cathignol et al. 1995; Tavakkoli et al. 1997; Chitnis et al. 2008). With these devices it is possible to design focal zones that are not only determined by the geometrical parameters of the source. Wave fronts that travel around the stone to enhance shear wave-generation inside the stone have been tested experimentally (Chitnis et al. 2008).

The first two piezoelectric tandem shock wave generators were based on *Piezolith 2300* shock wave sources (Loske and Fernández 2010). One of them was designed for in vitro studies (Loske et al. 2002b, c) and the other to evaluate the efficiency of tandem shock waves in vivo (Fernández et al. 2009a, b). Because the capacitors of these shock wave generators could not be charged with conventional power supplies

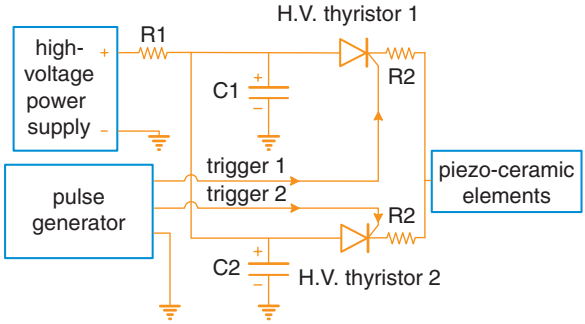


Fig. 5.56 Simplified diagram of the electric circuit to generate two underwater shock waves with a variable time delay using a single-layer piezoelectric shock wave source

in less than 50 ms, part of the electric circuit was duplicated (Fig. 5.56). A high-voltage power supply charges two capacitors (0.5 μF each), which remain charged until the first trigger switch is fired and the stored energy is discharged towards the piezoelectric elements. The second trigger is activated after certain delay to produce a second shock wave. Variable delays (50–950 μs) can be adjusted to emit tandem shock waves at a rate between 1 and 2.5 Hz (Fernández et al. 2005). To compare the in vitro fragmentation efficiency of conventional and tandem shock waves, standardized rectangular and spherical kidney phantoms were placed in small water-filled polyethylene bags at the focus of the experimental device (Loske et al. 2002b). The mass loss of the rectangular stone phantoms was significantly higher for tandem shock waves at a delay of 400 μs than for single-pulse shock waves. For spherical models significantly higher fragmentation efficiency was obtained for tandem shock waves at delays of 200 and 250 μs. In a following study, healthy rabbits were used as a model to compare in vivo renal tissue trauma produced by single-pulse and tandem shock waves (Loske et al. 2005). A histopathological analysis confirmed that tandem shock waves did not produce more trauma to the renal tissue than standard shock waves. A reason for this seems to be that cavitation nuclei are uncommon in soft tissue. Furthermore, because bubble expansion in vivo is constrained by the tissue, bubble collapse is less violent than in water or urine. Rabbits were used for this study because they are considered as valid animal models to evaluate shock wave-induced trauma to the kidney (Karalezli et al. 1993; Gunasekaran et al. 1989).

To demonstrate the importance of fluid surrounding the stone during SWL, small stone phantoms were inserted ex vivo into the parenchyma of pig kidneys and exposed either to single-pulse or tandem shock waves (Fernández et al. 2009a). Stones in the first group were placed inside a water-filled finger cot before being implanted while stones in a second group were implanted without fluid surrounding them. Only in the first group were tandem shock waves significantly more efficient in pulverizing stones than standard shock waves. The best results were achieved at a delay of 250 μs. The outcome of this study confirms that tandem shock waves improve stone comminution by enhanced acoustic cavitation.

In vivo treatments were performed as a next step to evaluate the feasibility to use tandem shock waves for SWL (Fernández et al. 2009b). Small artificial kidney stones were implanted into the parenchyma of the left kidney of 50 rabbits. The results

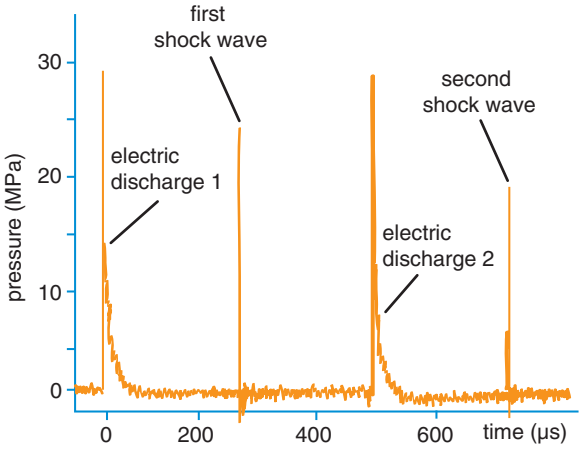


Fig. 5.57 Pressure profile emitted by a *Piezolith 2501*-based (Richard Wolf GmbH, Knittlingen, Germany) tandem shock wave generator at 4 kV. Both electric discharges appear as spikes on the screen of the oscilloscope and should not be confused with pressure pulses

confirmed the importance of fluid surrounding the stone in both single-pulse and tandem SWL. Furthermore, using tandem SWL it was possible to reduce the treatment time by up to 50 %. These were encouraging results; however, more studies are needed before using tandem shock waves clinically.

The success achieved with the aforementioned systems, motivated the design of another tandem shock wave source for in vitro studies, including experiments with microorganisms (Chap. 7), based on a *Piezolith 2501* transducer (Richard Wolf GmbH). A Lucite water tank with an xyz positioner was placed on top of the shock wave generator. The capacitor charging unit is similar to that described previously. A water cooling system was designed to reduce the temperature around the focal spot down to 1 °C. Mean peak-positive and peak-negative pressure pulses of approximately 26 MPa and −2.5 MPa, respectively, were recorded at the focus using a polyvinylidene difluoride (PVDF) needle hydrophone (Imotec GmbH) at a discharge voltage of 4 kV. In the tandem mode, the positive and the negative phase of the second shock wave were approximately 26 and 14 % smaller, respectively, than the positive and negative pressure amplitudes of the leading shock wave. A typical pressure profile recorded with this shock wave source is shown in Fig. 5.57.

As mentioned before, double-layer piezoelectric shock wave generators were developed by Richard Wolf GmbH (Dreyer et al. 2000; Riedlinger et al. 2002). These shock wave sources are the main element of the modular *Piezolith 3000* extracorporeal lithotripter and the portable *Piezoson 100 plus* designed for ESWT (Ginter and Krauss 2007; Ginter et al. 2010). Two piezo-ceramic layers are mounted on a bowl-shaped spherical backing (Fig. 5.58). Each layer is excited by an independent high-voltage circuit. Accurate power thyristor switches ensure that the front layer receives an electric discharge a short time after the back layer. Because of this, the impulses generated by both layers superimpose additively at the surface of the shock wave source. The superposition of the pressure pulses produced by each layer compensates for the pressure loss due to the smaller size of the dish, compared to the old single-layer models. Advantages of the double-layer shock wave source are

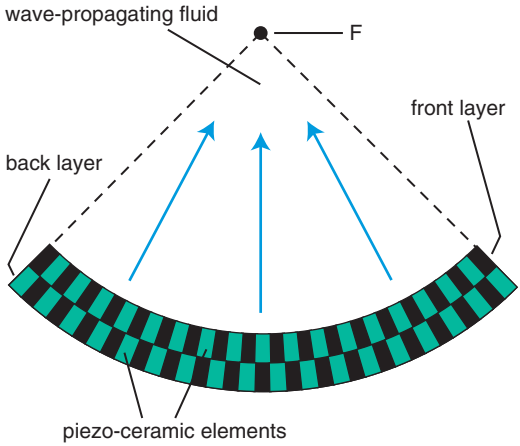


Fig. 5.58 Schematic of a double-layer piezoelectric shock wave source

its reduced weight and the fact that the delay between piezo-ceramic layers can be varied according to specific clinical needs. Shifting the delay widens the focal zone and reduces the amplitude of the peak pressure. As with mono-layer piezoelectric sources, the noise level is very low.

A modern representative piezoelectric lithotripter is the *Piezolith 3000 plus* (with triple focus) shown in Fig. 5.2. It has an isocentric design, consisting of a patient treatment table, a shock wave transducer in double-layer technology (aperture 270 mm; focal distance 165 mm; focusing angle 74°) and an X-ray C-arm. An in-line ultrasound scanner allows continuous monitoring shock wave coupling, stone fragmentation, and patient movements. Dual simultaneous real-time imaging as well as ultrasound or X-ray on-screen navigation with automatic coordinate transformation from a two-dimensional image to 3D-vector positioning is possible. Three different focus settings (*F1*, *F2*, and *F3*) are available to adjust the pressure field to a specific stone location, size, and composition. Fine focusing and high energy density is achieved using the *F1* setting. The *F1* setting of the *Piezolith 3000* with triple focus and the *Piezolith 3000 plus* corresponds to the standard setting of the first model (*Piezolith 3000*). In this case the contribution of both layers is superimposed so that the pressure on the surface of the shock wave source is maximal. In the *F2* and *F3* mode the back layer is fired 1.8 and 3.5 µs before the front layer, respectively. The *F3* setting is designed to have reduced peak-pressure and low EFD to guarantee "soft" treatments. The total energy at the focus remains approximately constant for the *F1* and *F2* settings. Pressure measurements recorded by the manufacturer on the *Piezolith 3000 plus* with an FOPH (RP Acoustics) according to the IEC standard 61846 revealed that the peak-positive pressure p^+, the EFD, and the total energy inside the 5 MPa focal zone may be varied from 7 to 125 MPa, 0.1 to 3 mJ/mm^2, and 3 to 240 mJ, respectively. The −6 dB focal zone can be considered to have the shape of a cigar with a diameter of approximately 3.7, 4.8, and 8.7 mm for the *F1*, *F2*, and *F3* setting, respectively. In vitro stone phantom fragmentation tests reported by Neisius (2006) revealed that if precise targeting is guaranteed, a small focal zone

with high shock wave energy density can be more efficient than a large focal zone. This should be considered when treating stones in the ureter, because the ureters are more resistant to shock wave trauma. Furthermore, stones in the ureter move less during respiration, being easier to target.

Bölles (2014) analyzed the results of 288 patients with urinary calculi after SWL using a *Piezolith 3000* with triple focus. All treatments were initiated with the *F1* setting by increasing the energy up to the pain threshold of each patient. A larger focal zone was selected after 500 shock waves. Ureteral stones were treated with the *F2* focus and renal stones with the *F3* focus. Treatments were performed without analgesia, sedation, or anesthesia, locating the stones via in-line ultrasound. Fluoroscopy was used to position the ureteral calculi at the focus. The energy level could be increased further when using the *F2* and *F3* focal zones, because less pain was reported by the patients than using the small *F1* focus setting. All patients received mechanical percussion to assist the passage of stone fragments after SWL. The achieved EQ, modified EQ (Sect. 5.6.12), re-treatment rate, and SFR for ureteral and kidney stones smaller than 10 mm was 0.72, 0.56, 1.15, and 92.2 %, respectively. Comparing the results reported by Bölles in 2014 with those published by Müller in 2002, it is evident that the *Piezolith 3000* with triple-focus is more efficient than the original *Piezolith 3000* having only the small *F1* focal zone. When using small focal zones, respiration may cause the stone to move out of the target zone and influence treatment outcome; however, improved localization techniques and anesthetic manipulation have been used to compensate for this. Excellent results were achieved with children, using *F1* (Goktas et al. 2011). Other encouraging results obtained with the *Piezolith 3000* can be found in the literature (Neisius 2006; Wang et al. 2009a).

In principle, double-layer shock wave heads could be suitable for generating tandem shock waves (Ginter and Krauss 2007). This possibility was evaluated with

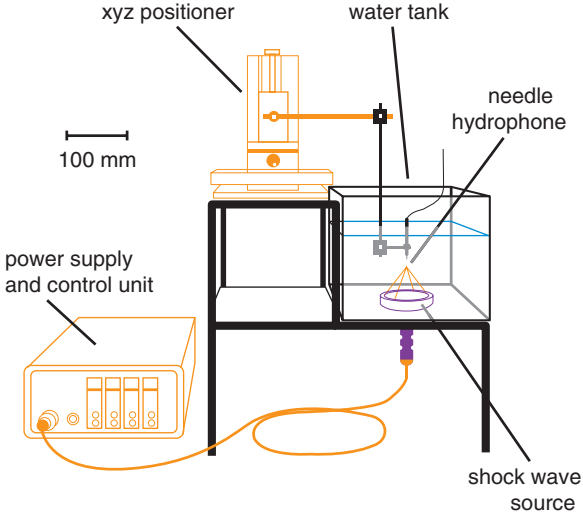


Fig. 5.59 Schematic of a *Piezoson 100 plus*-based research device (Richard Wolf GmbH, Knittlingen, Germany)

a *Piezoson 100 plus* shock wave head (Fig. 5.59) and reported by Lukes et al. (2015). The first pressure records were obtained by exciting only the front layer of the shock wave generator, a second group of measurements were done by exciting only the back layer; and the third set was obtained with both layers operating at the delay set by the manufacturer. Three intensity levels were evaluated in each mode. The highest pressure amplitudes were obtained in the standard mode. As expected, when the front layer was turned off, the pressure generated by the back layer was significantly lower than the pressure amplitude produced by the front layer alone. Although the *Piezoson 100 plus* was designed for ESWT (Sect. 6.2), its in vitro stone phantom fragmentation efficiency was evaluated at each of five different modes: the back layer operating alone, the front layer operating alone, the standard mode, and two tandem modes (back layer activated before front layer and front layer activated before back layer). Seven different delays between 100 and 800 μs were tested for both tandem modes. The fragmentation coefficients for both tandem modes were significantly smaller than those obtained in the standard mode, suggesting that varying the delay between the excitation of the layers in this shock wave source did not improve fragmentation efficiency; however, these results should be confirmed with the *Piezolith 3000* plus shock wave head, which was designed mainly for SWL. Nevertheless, double-layer piezoelectric sources can produce tandem shock waves for SWL if both layers are triggered at delays of a few hundred microseconds while maintaining their original time shift.

Other authors converted a *Piezolith 3000* to trigger both layers independently at an arbitrary time and analyzed bubble cluster dynamics after tandem shock wave passage through degassed and deionized water (Arora et al. 2005). Their results showed a great influence in bubble formation for delays in the range of the duration of the shock wave. If the delays were increased, the second shock wave modified the spatial shape of the cavitation cluster. For longer delays, that is, when the second shock wave arrived after the bubble cluster generated by the first shock wave had already collapsed, bubble debris acted as new cavitation nuclei, generating even larger bubbles. These results reveal that the double-layer technology may have uses not only for SWL, but also for other biomedical applications, such as ESWT, cell transfection, and genetic transformation of microorganisms (Chaps. 6 and 7).

5.4.2 Non-Spherical Piezoelectric Shock Wave Sources

In most piezoelectric shock wave sources the piezoelectric elements are mounted on a spherical dish; however, different designs are possible. Shock wave sources with their piezo-ceramic elements arranged on a non-spherical backing are useful for other medical applications. Planar and linear piezoelectric shock wave sources are used in ESWT and will be described in Sect. 6.2. Other shock wave sources use a ring or cylindrical piezo-ceramic transducer to emit radial pressure waves that are focused by a parabolic reflector as described for electromagnetic sources.

5.5 Other Shock Wave Sources

Devices to generate shock waves for biomedical applications with systems different from electrohydraulic, electromagnetic, and piezoelectric have been developed. Laser shock wave sources are useful as research tools, microexplosive lithotripters have been used for SWL, and multichannel discharge lithotripters are expected to be on the market in the future. Shock wave sources designed to enhance fragmentation efficiency while reducing tissue damage during SWL, combining electrohydraulic and piezoelectric shock wave generation have also been proposed.

5.5.1 Laser Shock Wave Sources

Focused laser pulses have been used to generate shock waves and study cavitation phenomena in the past (Bell and Landt 1967; Vogel and Lauterborn 1988; Vogel et al. 1996a, b; Berthe et al. 1997; Noack and Vogel 1998; Akhatov et al. 2001; Brujan et al. 2001a, b; Hosseini and Takayama 2004; Brujan 2008; Lauterborn and Vogel 2013). The first thorough step-by-step description of laser induced liquid breakdown and cavitation was published by Felix and Ellis (1971). It was followed several years later by a classical report on the dynamics of laser-produced cavitation bubbles published by Hentschel and Lauterborn in 1982. Lauterborn and Vogel (2013) also described the physics of laser pulses focused into liquids, addressing bubble dynamics. Their study included measurement of shock wave emission from bubbles collapsing near a boundary. Analogous to spark-gap systems, focusing of a laser beam in water produces dielectric breakdown, plasma formation, shock wave emission, and cavitation. Only a low percentage of the incident optical energy is converted into mechanical energy to produce the shock wave. If the laser is weakly focused, many bubbles are formed along the optical axis. Laser induced shock waves have only found application in SWL research; however, intracorporeal laser lithotripsy using flexible fiber-optic ureteroscopes became very popular (Rink et al. 1992, 1995; Vogel 1997; Zhong et al. 1998b). Experiments to study the feasibility of a laser extracorporeal lithotripter were done in the past. Andreev et al. (1992) reported in vitro fragmentation tests with an optoacoustic shock wave generator. A pulsed neodymium-glass laser was directed onto the window of the generator containing a thin surface of liquid with a high optical absorption coefficient. The liquid was heated, radiating a pressure pulse. Focused shock waves were generated because the boundary of the absorbing liquid had a spherical shape (radius 30 mm). The stone to be fractured was placed at the center of the spherical liquid foil.

Sankin and colleagues (2008) numerically and experimentally investigated the focusing of shock waves generated by optical breakdown in water at the first focus (*F1*) of a truncated ellipsoidal brass reflector using a neodymium doped yttrium aluminum garnet laser (wavelength 1046 nm, pulse duration 5 ns). As in electrohydraulic

shock wave sources, the shock wave produced at *F1* converged towards *F2*. The p^+ and p^- values reported by the authors were approximately 26 and −3 MPa, respectively. In contrast to spark-gap systems, the amplitude of the shock wave registered after the collapse of the laser-generated plasma bubble at *F1* is similar in amplitude to that of the initial shock wave produced by the optical breakdown. In an electrohydraulic shock wave source, the shock wave produced by the collapse of the plasma bubble at *F1* is weaker than the original shock wave. This may be due to the non-spherical collapse of the plasma bubble at *F1*, caused by the presence of the spark-plug. Another significant difference compared to electrohydraulic systems is that the −6 dB focal size of a laser shock wave source is smaller. Laser shock wave sources are used in research facilities to generate cavitation and may generate reproducible pressure pulses; however, their cost is high, making them less feasible for commercial lithotripters. Furthermore, at high energies the plasma gets elongated, spreading the acoustic energy and limiting the increase in peak pressure at the focal spot.

5.5.2 Microexplosive Shock Wave Sources

Early studies on biomedical applications of microexplosives were done in Japan by Murata et al. (1977) and Kaneko et al. (1979). These were followed by a collaboration between the Shock Wave Research Center and the School of Medicine of the Tohoku University to study the feasibility of microexplosive SWL (Takayama 1993). After successful in vivo experiments, the first patients with stones in the upper urinary tract were treated in 1985 using a microexplosive lithotripter (Kuwahara et al. 1986). A 10 mg lead azide pellet, placed at the closest focus (*F1*) to a paraellipsoidal metallic reflector generated spherical shock waves that reflected off the mirror and were focused as in an electrohydraulic shock wave lithotripter (Kuwahara et al. 1987). Each explosive pellet was attached to a metallic pipe and placed at *F1* by inserting the pipe into the reflector. The pellets were detonated by an igniting bridge connected to an 18 V battery. A disadvantage was that the pipe had to be replaced manually before each shock wave generation. During treatment, the patient was sitting on a chair inside a water tub (Fig. 5.60). Stone localization was achieved by obtaining two X-ray images with a horizontal X-ray C-arm. The chair could be electrically moved along three perpendicular axes. Depending on the size of the stone, between 50 and over 300 shock waves were generated per session. Epidural anesthesia was used in all cases. The SFR three months after treatment was 82 %; however, 27 % of the patients required combined treatment with percutaneous and/or transurethral lithotripsy.

Another report of microexplosive SWL was published by Honda et al. (1989). A total of 66 shock wave treatments for upper urinary tract stones were performed on an *SZ-1* lithotripter manufactured by the Japanese company Yachiyoda Co. Ltd. The lithotripter used 10 mg silver azide pellets as an energy source. Depending on the size of the stone, between 100 and 400 shock waves were needed. No anesthesia

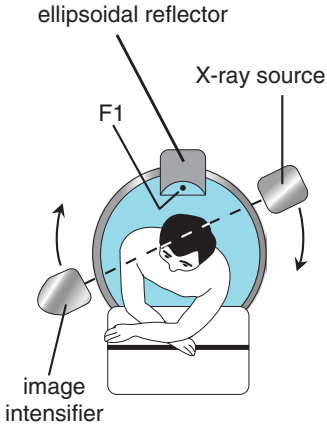


Fig. 5.60 Schematic of the first microexplosive extracorporeal shock wave lithotripter, showing the patient sitting on an electrically movable chair inside a water bath. Adapted from Kuwahara et al. (1987)

was required. Three months after SWL 57 % of the patients were stone free. Four percent of the patients required transurethral stone manipulation after SWL. The performance of a newer lithotripter model produced by this company, the *SZ-5000*, was reported by Saiko and Saito (1994). The device included ultrasound and fluoroscopy imaging. Sixteen stones in the renal pelvis, five in the ureteropelvic junction, nine in the upper, one in the middle, and three in the lower ureter were treated with approximately 350 shock waves. An 85 % SFR was reported three months after extracorporeal microexplosive lithotripsy (EML). The *SZ-5000* was not only used to comminute urinary stones. Ise et al. (1995) published the results of 30 gallbladder calculi patients treated with this device. Depending on the type of stones, the SFR varied between 40 and 100 %. Side effects and complications were reported to be mild.

Microexplosive generation of underwater shock waves was reliable and may have advantages for certain experimental purposes; however, it did not become popular in clinical practice. Automatically replacing the microexplosives at *F1* is a technological challenge, and the storage of explosives in a hospital, an additional inconvenience.

5.5.3 Combined Shock Wave Sources

To enhance stone comminution during SWL, Xi and Zhong (2000) implemented eight individual disk-shaped piezoelectric elements around the ellipsoidal reflector of an *HM3* lithotripter. The arrangement produced a second pressure pulse to enhance the collapse of bubbles induced by the initial shock wave. The *HM3* reflector and the piezoelectric array were mounted inside a Plexiglas tank filled with degassed water. Each shock wave transducer had its own high-voltage pulse generator. The piezoelectric array could be fired at a preset delay after discharging the spark-gap of the *HM3*-based shock wave source. The peak-positive pressure generated by the eight piezoelectric transducers at a voltage of 15 kV was approximately 8 MPa.

This pressure pulse was not sufficiently strong to comminute stone models in vitro; however, stone fragmentation was significantly improved if the second pressure pulse arrived during the collapse of the bubbles generated by the leading shock wave produced by the electrohydraulic shock wave source (24 kV). An increment of up to 80 % in stone fragmentation was achieved using the combined shock wave generator on kidney stone phantoms. This technical upgrade, and the reflector insert described in Sect. 5.2.1 (Zhong and Zhou 2001), were implemented into one single *HM3*-based dual-shock wave system (Zhou et al. 2004b). The reflector insert previously used to reduce injury inside blood vessels was not modified. An arrangement of six spherically concaved segments of piezocomposite material with a central resonant frequency of 230 kHz was fitted around the *HM3* reflector (Fig. 5.34). The piezoelectric segments, driven by a separate high-voltage generator, produced an independent second shock wave of approximately 13 MPa. Because of its small pressure amplitude, this wave was not expected to increase tissue damage. Furthermore, the focus of the piezoelectric source was much smaller than the focus of the *HM3* reflector, so that intensified bubble collapse was induced only in a small region around the stone. The main disadvantage of this system is that two shock wave sources are required.

5.5.4 Multichannel Discharge Shock Wave Sources

Multichannel discharge shock wave sources generate cylindrical pressure waves by underwater pulsed electrical discharges (Lukes et al. 2008, 2014). A large number of low-current pulsed discharge channels are produced at the surface of a cylindrical metallic electrode (60 mm in diameter and 100 mm long) covered with a thin porous ceramic layer and immersed in highly conductive water (15–20 mS/cm). Each discharge channel propagates through the liquid towards a metallic parabolic reflector. The focal point of the reflector is located 70 mm above its aperture. The electrode serves as the anode and the reflector as the ground electrode (Fig. 5.61). A ceramic

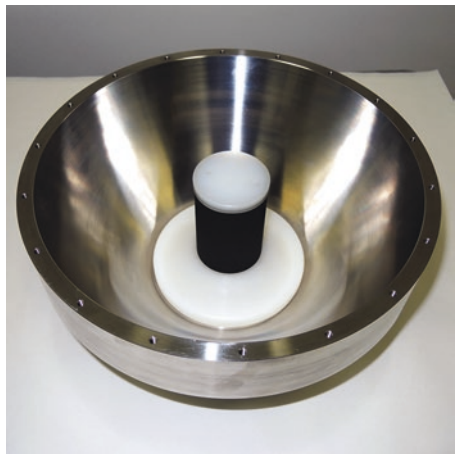


Fig. 5.61 Photograph of a stainless steel parabolic reflector and a cylindrical electrode coated with a porous ceramic layer, designed to generate focused shock waves using multichannel electrical discharges. (Courtesy of P. Lukes)

layer redistributes the electric field on the electrode during the pre-discharge phase. No spark/arc discharges are generated at voltages between 20 and 30 kV. The electrical circuit mainly consists of a high-voltage direct current power supply used to charge a 0.8 μF capacitor, and a spark-gap switch and trigger unit to control the discharge rate. The difference in conductivity and permittivity between the highly conductive water and the ceramic layer increases the electric field strength on the surface of the electrode, facilitating the generation of discharge channels on the whole electrode. Each discharge channel has a length of less than one millimeter (Fig. 5.62) and creates a semi-spherical pressure wave in the liquid. Superposition of these waves produces a cylindrical pressure pulse propagating from the composite electrode perpendicular to the cylinder axis. The pressure wave is focused by the parabolic reflector, steepening into a shock wave in the neighborhood of the focal spot. As shown in Fig. 5.63, the device consists of two sections divided by a Mylar foil.

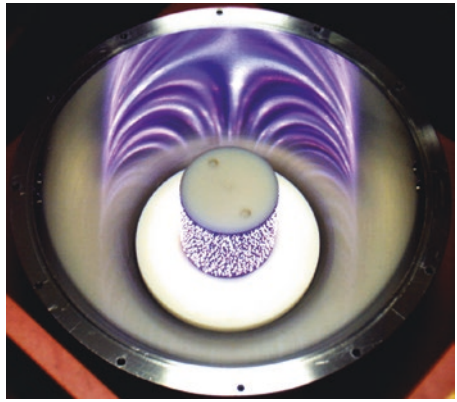


Fig. 5.62 Photograph of multichannel pulsed electrical discharges at the surface of a cylindrical metallic electrode covered with a porous ceramic layer, immersed in conductive water. (Courtesy of P. Lukes)

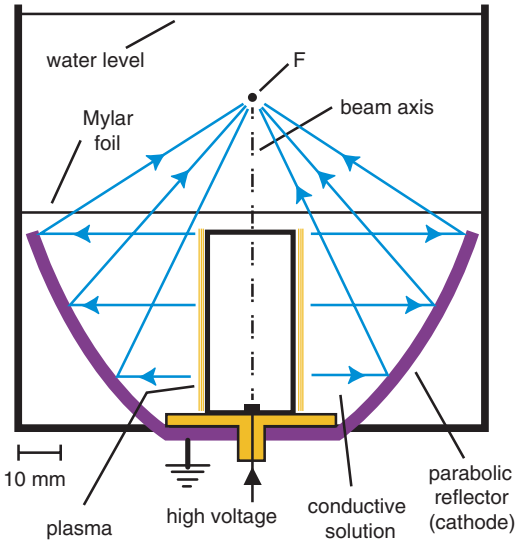


Fig. 5.63 Schematic diagram of a multichannel discharge shock wave source consisting of a cylindrical composite electrode coated with a porous ceramic layer placed along the axis of symmetry of a parabolic reflector to concentrate underwater shock waves at the focus *F*. Adapted from Lukes et al. (2015)

The lower section contains the high conductivity solution and the upper section is filled with tap water. Higher pressures can be obtained by increasing the conductivity of the water, because plasma of higher power density is produced (Sunka 2001; Stelmashuk and Hoffer 2012). These shock wave sources generate pressure profiles similar to electrohydraulic generators; however, higher peak-positive pressures and a very small focal volume have been reported. Lukes and colleagues recorded pressure measurements on their multichannel discharge shock wave source using a fiber-optic hydrophone (*FOPH 2000*, RP Acoustics). At a discharge voltage of 21 kV and a capacitance of 0.8 μF, the registered positive pressure was $p^+ = 372$ MPa with a phase duration of 1.5 μs. The peak amplitude of the negative pressure phase was −17 MPa with a duration of 2 μs (Lukes et al. 2014). Pressure measurements recorded at 1 mm steps perpendicular to the axis of the reflector at the height of the focus F revealed that the −6 dB focal zone measures 0.5 mm in diameter, that is, the pressure amplitude dropped to 50 % of p^+ at a distance of less than 0.25 mm from the axis of the reflector.

Multichannel discharge shock wave generators have also been used to emit tandem shock waves (Stelmashuk and Sunka 2006; Sunka et al. 2006; Lukes et al. 2014). As shown in Figs. 5.64 and 5.65, the system uses two cylindrical electrodes of different diameters. A high-voltage discharge is applied to both electrodes, either separately through two spark-gaps using two capacitors and two power supplies or simultaneously using one trigger switch and one capacitor. The lower electrode has a diameter of 90 mm and a length of 17 mm, and the upper electrode has a 60 mm diameter and is 55 mm long. As in the single-pulse multichannel discharge shock wave generator, both metallic electrodes are covered with a thin porous ceramic layer. In this arrangement, two successive shock waves focused at a common focal point with a time delay between the waves on the order of microseconds are generated.

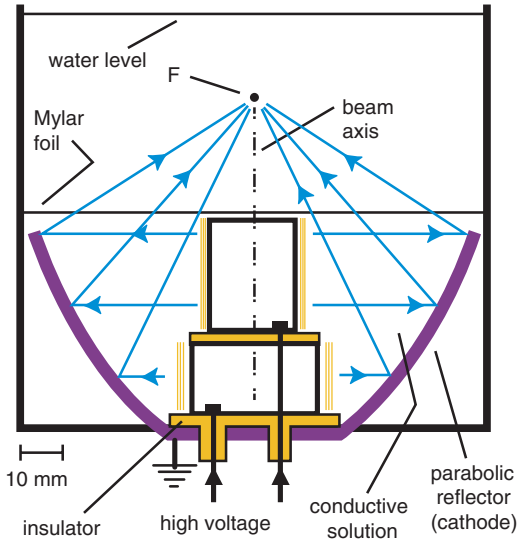


Fig. 5.64 Schematic diagram of a multichannel discharge tandem shock wave source consisting of two cylindrical composite electrodes coated with a porous ceramic layer placed along the axis of symmetry of a parabolic reflector to concentrate underwater shock waves. Adapted from Lukes et al. (2016)

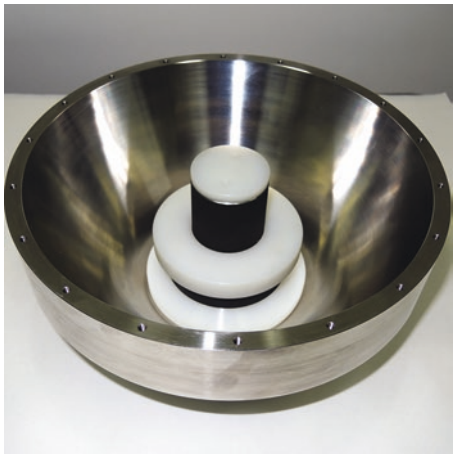


Fig. 5.65 Photograph of a stainless steel parabolic reflector with two cylindrical electrodes coated with a porous ceramic layer, designed to generate focused tandem shock waves using multichannel electrical discharges. (Courtesy of P. Lukes)

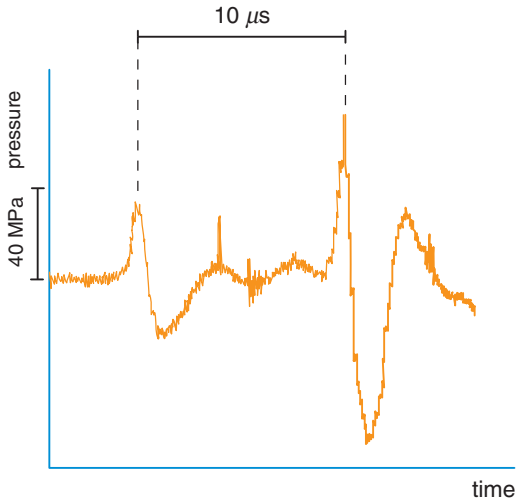


Fig. 5.66 Pressure profile of a tandem shock wave (delay 10 μs), recorded with a PVDF needle hydrophone at the focus of a multichannel discharge shock wave source (capacitance 0.8 μF, voltage 30 kV). The first shock wave arrived at *F* after approximately 148 μs. Adapted from Lukes et al. (2014)

The positive peak-amplitude of the second shock wave can reach up to 100 MPa, with a rarefaction phase of down to as much as −80 MPa (Lukes et al. 2014).

Using tandem multichannel discharge shock wave generators, the pressure profiles of both focused shock waves can be adjusted, to a certain extent, by varying the geometry of the electrodes, the capacitance of the capacitors, the discharge voltage, and the conductivity of the saline solution in the lower section of the shock wave source. The time delay between the first and second shock wave can be adjusted either electronically or by changing the diameters of one or both electrodes. Further variations can be achieved designing a different parabolic reflector; that is, by varying the distances from the electrodes to the focus. Using the electrode diameters mentioned above, the path lengths differ by 15 mm. This corresponds to a delay of approximately 10 μs between the arrival of the first and second shock wave at *F*. Figure 5.66 shows a pressure waveform recorded at the focus *F* at a time delay of

10 μs between the two shock waves. Pressure measurements and schlieren photography revealed that when the second shock wave was emitted 8–15 μs after the leading shock wave, a complex pressure field was observed in the focal region. The pressure records at *F* showed a large amplitude rarefaction wave (Stelmashuk and Sunka 2006; Sunka et al. 2006; Lukes et al. 2014).

Multichannel discharge shock wave sources may be introduced into several clinical applications in the near future. An extracorporeal lithotripter having a multichannel discharge shock wave generator was already developed and is being tested at the Institute of Plasma Physics of the Academy of Sciences of the Czech Republic. Contrary to the devices described above, the novel multichannel discharge extracorporeal lithotripter does not use two divided sections, one with a saline solution and the other section with water. Instead of this, the water tank of the lithotripter is only filled with saline water and the patient's skin is directly in contact with it.

5.6 Shock Wave Lithotripsy in Urology

Urolithiasis, i.e., the ailment where urinary stones are formed anywhere within the urinary tract, is a major problem for healthcare systems in most countries. International epidemiological data suggest that, probably because of increasing levels of obesity and metabolic syndromes, urolithiasis is increasing globally (Menon et al. 1998; Stoller and Bolton 2000; Kerbl et al. 2002; Pearle et al. 2005; Curhan 2007; Sas 2010; Turney et al. 2011; Knoll and Pearle 2013). Kidney stones affect up to 10 % of the population in the USA (Scales et al. 2012). Between 1976 and 1994, the prevalence of urolithiasis increased from 3.8 to 5.2 % (Stamatelou et al. 2003). Based on data from the National Health and Nutrition Examination Survey (NHANES), there was a further increase from 5.2 % in 1994 to 8.9 % in 2008 (Scales et al. 2012). In Germany during the year 2000 about 9.7 and 5.9 % of all 50 to 64-year-old males and females, respectively, had urinary stones and the recurrence rate was approximately 42 % (Hesse et al. 2003).

Before SWL was introduced into clinical practice in 1980, an open surgery (*lithotomy*) with long recovery period was the only existing procedure for kidney stones that could not pass spontaneously through the urinary tract. Nowadays, open surgery is extremely rare for the management of urological stone disease and not only SWL, but also minimally invasive techniques allow removing almost any urinary stone.

Minimally invasive endoscopic treatments to remove stones have changed the clinical practice to treat stones over the last 30 years. Despite PCNL and ureteroscopy, SWL is still the primary treatment for most renal stones less than 15 mm, and an alternative in the treatment of proximal stones, and midureteral stones less than 10 mm, because it exposes patients to less anesthesia, is easy to perform, safe, and minimally invasive (Tailly et al. 2008; Chi-fai 2009; Bergsdorf and Chaussy 2010; Bach and Buchholz 2011; Buchholz et al. 2011; Bach et al. 2012; Bader et al. 2012; Rassweiler et al. 2012; Paonessa and Lingeman 2014; Chaussy and Tiselius 2015;

Schnabel et al. 2015). SWL remains the only noninvasive modality in lithotripsy and still contributes to more than half of all urinary stone treatments worldwide (Bach and Buchholz 2011). The reported success rates vary significantly because different lithotripters, definitions of success, and protocols were used (Renner and Rassweiler 1999; Rassweiler et al. 2001; El-Assmy et al. 2006a; Galvin and Pearle 2006; Matlaga and Semins 2009; Steinberg et al. 2010; Elkoushy et al. 2011; Abid 2014). SWL proved to be an option to treat high-risk patients and patients in whom other procedures were not feasible (Tiselius et al. 1999; Chaussy and Tiselius 2012; Tiselius and Chaussy 2012). According to Chaussy et al. (2014), SWL is recommended as the first-line therapy to remove radiopaque (calcium) and cystine stones with a maximum diameter of 20 mm. SWL is also safe to treat pediatric patients (Goktas et al. 2011; Ozgür et al. 2016; Akin and Yucel 2014) and considered as the most convenient option for geriatric patients (Sighinolfi et al. 2008; Philippou et al. 2012). Ureteroscopy is known to achieve a higher SFR than SWL; however, more potential complications and longer hospital stays are associated with it (Aboumarzouk et al. 2012). An additional advantage of SWL is the possibility to use intravenous sedation or minimal anesthesia, as well as a greater probability of not needing a ureteral stent. Moreover, percutaneous techniques (accepted as the method of choice for stones larger than 20 mm) and SWL should not be considered as competing to each other. It has been realized that the combination of both may have advantages. The European Association of Urology recommends SWL, with its success rates varying from 60 to 90 %, as the method of first choice for stones smaller than 20 mm within the renal pelvis, upper or middle calices, for stones smaller than 15 mm within lower pole calices and for upper ureteric stones smaller than 10 mm (Türk et al. 2015). The German guidelines (Miernik et al. 2012) and the American Urological Association (AUA) recommend SWL as the primary treatment modality for several stone types. Its outcome depends on several factors, such as the stone size, shape and composition, the stone impaction, the shock wave generator, the imaging system, anatomical abnormalities, the existence of a fluid filled expansion chamber, the shock wave rate and energy, the use of pre-SWL procedures, and last but not least the expertise of the operator. If patients are selected adequately, the success rate of SWL for stone clearance can be excellent (Montag et al. 2010).

Pre-operative studies normally include a renal ultrasonography, a non-contrast computed tomography (NCCT) scanning, an anticoagulation profile, a blood cell count, and a urinalysis, with urine culture. An intravenous pyelogram (X-ray examination using a contrast agent to obtain information on the anatomy and functioning of the renal system) is rarely required.

5.6.1 Contraindications

Contraindications to SWL are acute urinary tract infection or urosepsis, kidney cancer, obstruction distal to the stone, life-threatening cardiac problems, uncorrected coagulation abnormalities, and active pyelonephritis. Pulmonary tissue, a tumor, pathological changes, or an aneurysm in the shock wave path are also

contraindications (Chaussy et al. 2014). If the patient prefers SWL, even hard stones such as brushite and cystine stones are not a contraindication for SWL as long as the stone burden is small (Chaussy et al. 2014). Malformations of the kidney, renal insufficiency, hypertension, spinal deformities and a compromised mental status of the patient, and the inability to cooperate may be contraindications.

Patients are advised to discontinue anticoagulants, aspirin-containing products, and nonsteroidal anti-inflammatory drugs several days before SWL, so that their clotting factors return to normal values. Pregnancy is considered a contraindication because of the possible adverse effects of fluoroscopy and shock waves on the fetus. There are some clinical results revealing that ultrasound-guided SWL of renal calculi during early pregnancy should not be a cause for concern (Asgari et al. 1999). Nevertheless, the authors of this study admitted that a larger series should be assessed to confirm the safety and long-term effects of SWL in the treatment of renal calculi during pregnancy.

In some cases, dysrhythmias may occur during shock wave treatment; however, they can be controlled by gated SWL, i.e., synchronizing the shock wave emission with the *R* wave (refractory period of the cardiac cycle). The need for synchronized or gated shock wave emission is less in children. Shouman et al. (2009) treated children younger than 14 years with radio-opaque renal stones by ungated SWL. Their results suggest that ungated extracorporeal lithotripsy is safe in children. Treatment outcomes were comparable to that of gated SWL from previous studies. ECG monitoring is recommended for patients with preexisting arrhythmia (Kataoka 1995). Cardiac pacemakers are normally not considered as contraindicated; however, patients with a pacemaker require special attention. If approached cautiously, SWL can be performed in patients with an aortic aneurysm (Thomas et al. 1991). Patients with an automatic implanted cardioverter defibrillator have been successfully treated with SWL; however, special care should be taken and a post-procedure evaluation to ensure appropriate function of the device is important (Venditti et al. 1991; Vassolas et al. 1993; Küfer et al. 2001). Prior to SWL, the attending cardiologist should be consulted. For safety reasons, implanted cardioverter defibrillators need to be switched off before treatment and switched on immediately after treatment. Continuous ECG recording is recommended during SWL. Evidence-based guidelines on this topic have been reported by Platonov et al. (2008). Finally, it should be commented that cystine or calcium oxalate monohydrate stones, stones larger than 20 mm, stones in the inferior pole, morbid obesity, and obstructed collecting systems (calyceal diverticulae, uretero-pelvic junction obstruction, and horseshoe kidneys) may be causes of poor fragmentation efficiency or poor stone clearance after SWL.

5.6.2 Pediatric Patients

It is known that adult males are more frequently affected by urolithiasis than females; however, in children, there is an equal tendency in both genders (Menon et al. 1998). SWL has been reported to be safe and successful to treat urolithiasis in children. Fayad and colleagues (2012) reported no significant differences when comparing the

renal growth in SWL-treated children with a control group that did not receive shock waves. Villányi et al. (2001) studied the short-term effects of shock waves on renal function in children by measuring sodium, potassium, urea, creatinine, and C-reactive protein in blood, urinary electrolytes, urinary enzyme activity, and the excretion of b2-microglobulin before, 2 h after SWL, and on days 1, 2, 8, 15, 30, and 90 after treatment. No morphological changes in the kidneys could be detected by ultrasound and no significant changes were observed in the renal function, serum parameters, or urine electrolytes. However, an elevation in the excretion of aspartate transaminase, alkaline phosphatase, lactate dehydrogenase, and b2-microglobulin revealed proximal tubular dysfunction and destruction of cells. The enzyme levels returned to normal values after 2 weeks. An important conclusion of this study was that the minimal interval between two SWL sessions should be at least 2 weeks.

A significant advantage of SWL in children is that the ureter is more elastic, facilitating passage of fragments (Chaussy et al. 2014); however, as in adults, stone size has been reported to be a crucial factor determining the stone-free rate (Tan et al. 2004; Wadhwa et al. 2007). Most authors recommend SWL for children (Newman et al. 1986; Thomas and Sosa 1998; Marberger et al. 1989; Abara et al. 1990; Starr and Middleton 1992; Myers et al. 1995; Cohen et al. 1996; Lingeman 1997; Kroovand 1997; Lifshitz et al. 1998; Jayanthi et al. 1999; Choong et al. 2000; Elsobky et al. 2000; Schulz-Lampel and Lampel 2001; Alapont et al. 2002; Rodrigues Netto et al. 2002; Ather and Noor 2003; Muslumanoglu et al. 2003; Tan et al. 2004; Wese et al. 2003; Aksoy et al. 2004; Demirkesen et al. 2006; Shokeir et al. 2006; Skolarikos et al. 2006; da Cunha Lima et al. 2007; Nomikos et al. 2007; D'Addessi et al. 2008; Griffin et al. 2010; Lottmann et al. 2010; Straub et al. 2010; Goktas et al. 2011; Ozgür et al. 2016; Akin and Yucel 2014); however, during pediatric SWL it is important to consider that shock waves are passing through short distances of soft skin, losing less energy than in adults. Energy flux densities below 0.5 mJ/mm^2 are recommended for children. A study on the EQ (Sect. 5.6.12) of pediatric SWL at various locations in the upper urinary tract and a suggestion on modifications to the EQ in children were published by Hammad et al. (2009).

Some lithotripters require certain modification for pediatric use. The out-line scanner may be replaced for a 5 MHz scanner. Flexible apertures including reflectors for children are available on some models. The *Lithoskop* (Siemens Healthcare GmbH) electromagnetic lithotripter included a pediatric kit with a special gantry (Loske 2007; Lanski et al. 2010). Because of their large focal zone, care is needed when using standard electrohydraulic lithotripters for children and it should be considered that the non-reflected pressure wave (Fig. 3.8) could cause tissue damage. Special caution should be taken to protect the lungs from shock wave passage. This is crucial when treating upper pole stones. Shielding can be achieved using materials with low acoustic impedance, such as polystyrene or foam. If the patient is too thin to target the stone, saline bags may be needed to displace the shock wave source away from the stone; however, care should be taken to avoid air bubbles in the shock wave path.

5.6.3 *Obese Patients*

The penetration depth depends on the type of lithotripter, the model, and the manufacturer. Knowing the penetration depth is important, especially before treating obese patients. Obesity and extreme obesity are defined by a body mass index (BMI) greater than or equal to 30 and 40 kg/m^2, respectively. The probability of a high SFR in obese patients having large and hard stones is low. Contrary to pediatric SWL, when treating obese patients the large skin-to-stone distance (SSD) has been reported to reduce the probability of a good outcome (Pareek et al. 2005b; Patel et al. 2009; Graversen et al. 2011; Wiesenthal et al. 2011). Furthermore, obesity could be a contraindication for SWL because of excessive weight and technical difficulties in positioning the patient. Very obese patients can only be treated on few lithotripter models and successful outcomes are not easy to achieve. If the urinary stone of a morbidly obese patient cannot be placed at the focal spot, because the SSD exceeds the distance from the treatment cushion to the focus, it is recommended to place the stone along the so-called blast path, i.e., along the beam axis of the shock wave source (Fig. 5.67). Depending on the lithotripter, a few centimeters away from the focal spot, the shock wave energy along the beam axis may be sufficient to fracture the stone (Whelan et al. 1988). Fortunately nowadays lithotripters with penetrations depths of up to 170 mm are available (Chaussy et al. 2014). This is important in societies with an increasing proportion of obese patients. For instance, Mezentsev (2005) treated morbidly obese patients having renal pelvicalyceal stones and achieved an overall 3-month SFR of 73 %.

Experience has revealed that SSD predicts SWL results (Patel et al. 2009). Because SSD can be easily measured by non-contrast computed tomography (NCCT), showing adiposity and fat distribution, it may be a valuable tool to make pre-treatment decisions. Park et al. (2012) published the results of a study to determine the relationship between SSD obtained by computed tomography (CT), and the SFR achieved after SWL for urinary stones (5 to 20 mm). Successfully treated patients were defined

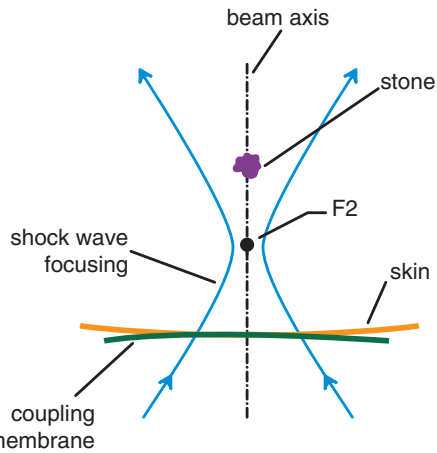


Fig. 5.67 Schematic of shock wave focusing and out-of-focus positioning of a kidney stone along the "blast path," during SWL of a morbid obese patient

as those whose stones had disappeared on a CT scan or simple X-ray within 6 weeks after shock wave treatment. The statistical analysis revealed that the success group had a significantly shorter SSD than the failure group. The results of the multivariate logistic regression analysis showed SSD to be the only significant independent predictor of the SWL stone-free rate, with a significant decrease in SFR when the SSD was greater than 100 mm. According to Ackermann et al. (1994) the BMI and the number of stones are the only significant predictors of SWL outcome.

Ng and colleagues (2015) performed a logistic regression analysis to assess if patient's age, shock wave rate, stone size, mean stone CT density (MSD), SSD, renal cortical thickness (KT), muscle thickness (MT), and soft-tissue thickness (ST) predict treatment outcomes. The study was performed on more than 200 patients having a 5–20 mm kidney stone treated with a *Sonolith Vision* lithotripter (EDAP TMS). As expected, their results showed that the volume and the MSD may help to predict SWL treatment outcomes; however, contrary to the information published by other authors, the SSD was not related to a successful SWL in a multivariate analysis. The KT revealed to affect treatment outcome, whereas MT and ST did not. The main conclusion of the study was that larger KT values are a favorable factor for successful SWL. From the physical standpoint it is reasonable to believe that SWL success is related to the composition of the tissues along the shock wave path.

To avoid exposure to ionizing radiation, bioimpedance analysis (BIA) has been proposed as an alternative. The technique uses low frequency current to measure the total body resistance. Graversen et al. (2011) prospectively collected body composition data using a body impedance analyzer on 52 consecutive patients who were undergoing SWL on the same lithotripter. Stone size, fat mass percentage (FMP), BMI, and SFR were correlated. BIA and BMI were significantly associated with success; however, only 37 patients were included in the study because of an inability to accurately assess success or failure after SWL in the remaining 15 patients. In another study, Hwang et al. (2014) reported that SWL failure for ureteral stones can be predicted when patients have a BMI larger than 25 kg/m^2. Wiesenthal et al. (2010) studied the influence of MSD and SSD on the success of 422 SWL-patients with a solitary renal or ureteric calculus smaller or equal to 20 mm in diameter. An MSD higher than 900 Hounsfield units (HU) (Sect. 5.6.10) and an SSD larger than 110 mm were significant predictors of outcome.

In the past, the STS lithotripter (Medstone International, Inc., Irvine, CA, USA) was used to successfully treat obese patients up to 40 mm away from the focal point (Thomas and Cass 1993). Another useful lithotripter to treat morbidly obese patients has been the Siemens *Lithoskop* with its *Pulso* shock wave source. Advantage has been taken of its increased focal width, its penetration depth of 160 mm and the high energy output (Bergsdorf et al. 2005b). Abdominal compression belts placed in the upper part of the abdomen are recommended in most cases (Tiselius and Chaussy 2012). They have shown to be useful not only to reduce stone movement due to respiration, but also to reduce the SSD in obese patients (Argyropoulos and Tolley 2007).

5.6.4 The Focal Size

As already mentioned, the debate in regard to the ideal focal zone of an extracorporeal lithotripter has not been solved. A reason for this is that depending on the focal size, different effects seem to play a crucial role. Shear forces and spallation are predominant fragmentation mechanisms in lithotripters with small focal sizes and circumferential squeezing plays a crucial role in shock wave sources with large focal zones. In vitro experiments and modeling elastic wave propagation in kidney stones revealed that the stress inside a stone increases with the −6 dB focal size (Cleveland and Sapozhnikov 2005; Sapozhnikov et al. 2007).

Large focal zones are produced by electrohydraulic shock wave sources and the smallest focal volumes by piezoelectric devices (Fig. 4.5). Most electromagnetic lithotripters generate focal zones with a size in-between of those produced by electrohydraulic and piezoelectric lithotripters (Fig. 5.68), except for the self-focusing electromagnetic shock wave source described in Sect. 5.3.4.

With the aim of reducing tissue trauma by applying less shock waves and concentrating the shock wave energy basically on the stone, some manufacturers designed shock wave sources that generate relatively high pressure amplitudes and a small focal zone (Moody et al. 2001). Lithotripters generating small focal zones allow treatments with minimal anesthesia; however, precise patient positioning is crucial when using these lithotripters, because there is little margin of error for targeting the stone.

Since breathing causes considerable stone displacement, synchronizing shock wave emission with the respiratory motion, as well as automatic stone-tracking systems can be helpful (Cathignol et al. 1995; Dawson et al. 1996).

During the 1990s, several reports revealed that new lithotripters were not as successful as expected (Knapp et al. 1988; Tan et al. 1991; Bierkens et al. 1992; Krishnamurthi and Streem 1995; Grenabo et al. 1997; Eichel et al. 2001) strengthening the idea to return to shock wave sources with wide focal zones, that mimic the pressure profile of the Dornier *HM3* (Pishchalnikov et al. 2013). The *MPL-9000X* (Dornier MedTech GmbH) could be used with two types of spark-plugs. The standard

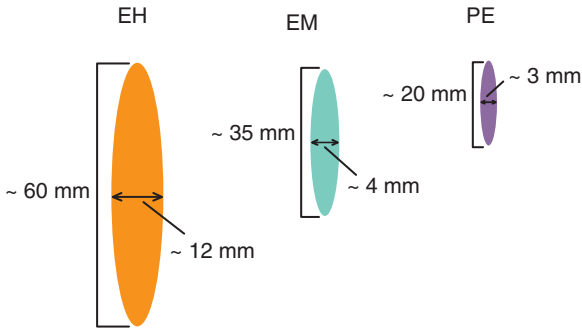


Fig. 5.68 Focal zones of electrohydraulic (EH), electromagnetic (EM), and piezoelectric (PE) shock wave lithotripters. The −6 dB focal zones have a shape similar to that of a cigar, with the lengths and diameters shown here

plug, and a spark-plug with the electrode tips 5 mm out of focus, providing an extended *F2* focal volume.

Examples of large-focus, low-pressure lithotripters are the *LithoSpace* (Jena Med Tech GmbH, Jena, Germany), the *LithoGold LG-380* (MTS Medical UG, Konstanz, Germany), and the *CS-2012A-3* (Suzhou XiXin Medical Instruments Co., Ltd, People's Republic of China). Qin et al. (2010) studied the effect of the focal size and the pressure amplitude on in vitro stone comminution by modifying the geometry of an original Dornier *HM3* reflector to produce a lithotripter field with high peak pressure and narrow beam size. Comparing the stone fragmentation efficiency of the conventional reflector with that obtained using the modified reflector on the *HM3*, they demonstrated that better stone comminution was obtained at low pressure with a wide focal size. This result is especially interesting because acoustic energy is known to correlate with stone fragmentation. In this experiment the stone phantoms in both groups were exposed to the same acoustic energy.

Some lithotripters, such as the *Piezolith 3000* (Richard Wolf GmbH) and the *Modulith SLX-F2 connect* (Storz Medical AG), allow adjusting more than one focal size. The common recommendation is to treat renal calculi with large focal zone settings and use the small focal zones to treat ureteral stones. Fortunately modern imaging systems facilitate precise patient positioning and, if targeting is precise, a small focus seems to be favorable both to treat kidney stones and stones in the ureter.

Information on the size of the −6 dB focal zone is not sufficient to characterize the pressure field. According to its definition (Sect. 3.4), the −6 dB focal zone includes the volume where the pressure is equal to or higher than half of the peak-positive pressure, regardless of the absolute peak pressure. Because of this, a shock wave source having a peak-positive pressure p^+ of 90 MPa could have the same −6 dB zone as a source producing a p^+ equal to 50 MPa.

If not specified, the focal-zone definition is related to the maximum peak-positive pressure (p^+); however, it does not necessarily coincide with the volume of clinical efficiency. As mentioned in Chap. 3, a focal zone based on the maximum peak-negative pressure (p^-) may also be useful. Because the negative phase of the shock wave influences bubble dynamics, a focal zone determined by the negative pressure amplitude could be a better indicator of fragmentation efficiency. In general, p^+ and p^--based focal zones do not coincide. In an electrohydraulic shock wave source the maximum peak-negative pressure is not located exactly at *F2*, but closer to *F1* and the fragmentation efficiency could be enhanced by placing the stone several millimeters in front of the geometrical focus of the lithotripter.

5.6.5 The Shock Wave Rate

Even if most lithotripters can deliver 240 shock waves per minute or more, high shock wave rates are not recommended. High shock wave emission frequencies enhance cavitation, and high output energies of the shock wave source increase the lifespan of cavitation bubbles (Delius et al. 1987; Huber et al. 1998, 1999a;

Sapozhnikov et al. 2002; Tanguay and Colonius 2003; Weizer et al. 2007). The fact that less shock waves are required to pulverize kidney stone phantoms at slow shock wave rates was reported by Paterson et al. (2002) and Pishchalnikov and colleagues (2006a). Lifshitz et al. (1997) showed that damage to aluminum foils placed at the focus of an extracorporeal lithotripter decreased significantly at high shock wave rates. Bubble dynamics recorded with high-speed cameras and B-mode ultrasound, revealed that close to a stone, or close to the particles released from it, the tensile phase of the shock wave was reduced significantly at higher shock wave rates, because cavitation nuclei persisted between one shock wave and the next. Even if these nuclei do not attenuate the positive pulse of a shock wave, its following pressure trough seeds cavitation bubbles. This requires energy from the negative pressure pulse, reducing its amplitude and the effectiveness of cavitation to pulverize the stone.

Greenstein and Matzkin (1999) demonstrated that significantly fewer shock waves were needed for complete in vitro fragmentation of spherical stone phantoms (mean diameter 9.5 mm) at a shock wave rate of 60 shock waves per minute compared to 90, 120, and 150 shocks per minute, using an electrohydraulic shock wave generator at 15, 20, and 22.5 kV. No statistically significant difference was found when comparing the in vitro fragmentation efficiency at 30 and 60 shock waves per minute. Madbouly et al. (2005) prospectively randomized more than 150 patients with a single renal or ureteral stone not exceeding 30 mm in diameter, to receive SWL at 60 shock waves per minute or 120 shock waves per minute, concluding that the slow SWL rate was associated with a significantly higher success rate at a lower number of total shock waves compared to the fast rate. In a randomized, double-blind study Pace et al. (2005) found that SWL at 60 shock waves per minute yielded better outcomes than at 2 Hz, particularly for stones 10 mm or greater, without any increase in morbidity. Chacko et al. (2006) reported that, for solitary renal stones between 10 and 20 mm in size, slow shock wave delivery produced better treatment results than fast rates; however, this difference became less significant for stones smaller than 10 mm. Another study, reporting the treatment of 134 patients with radio-opaque stones in the upper urinary tract, that were treated by 1 and 2 Hz-SWL, revealed that the slow rate therapy contributed to better stone comminution than fast rate-SWL, mainly for small stones and renal stones (Kato et al. 2006). In a meta-analysis Semins et al. (2008) found that patients treated at 1 Hz had a greater probability of a successful SWL outcome than patients treated at 2 Hz. More recently, Lee and Moon (2011) also reported better outcomes treating patients at a shock wave rate of 1 Hz compared to a frequency of 2 Hz. Koo et al. (2010) compared treatment outcomes and cost-effectiveness of SWL at 70 shock waves per minute with lithotripsy at 100 shock waves per minute. Included were 102 patients who had upper urinary tract radio-opaque calculi, treated on a *Lithotripter S* (Dornier MedTech GmbH) as an outpatient procedure with no anesthesia or sedation. Their conclusion was that the slow shock wave rate significantly improved treatment efficiency and reduced the cost of additional procedures to result in clinical success. Gillitzer and colleagues (2009) compared the fragmentation efficiency of standardized artificial kidney stones inserted into the renal pelvis of anesthetized pigs and treated at 1 and 2 Hz with 3000 shock waves on a *Lithoskop*

lithotripter (Siemens Healthcare GmbH). After nephrectomy all fragments were sieved and weighed. Results showed that the slow shock wave rate yielded significantly smaller fragments than those obtained after SWL at 2 Hz. The formation of renal hematomas was comparable in both groups.

Since acoustic cavitation may produce tissue injury, not only the number of shock waves (Delius et al. 1988b, 1990a, c), but also the shock wave rate (Delius et al. 1988d) influences tissue damage. Studying kidney hemorrhage in dogs at a fast shock wave administration rate (15 Hz) revealed that high frequencies produce important renal injury (Delius et al. 1990b). Several years later, Evan and colleagues (2007) confirmed that renal injury during SWL is significantly reduced by slowing the rate of shock wave delivery. It is important to mention that this effect seems to depend on the size of the focal zone. According to an in vivo study published by Connors et al. (2012), slowing the shock wave rate was not effective in reducing tissue injury when using a Storz *Modulith SLX*, which has a small focal zone compared to the *HM3*, in which reducing the shock wave rate is known to be effective to reduce tissue injury.

Because of the concern that SWL at fast rate on dual-head lithotripters could cause increased tissue damage, Handa et al. (2009b) assessed renal trauma in pigs treated with 2400 shock waves delivered in the alternating mode at a rate of 120 shock waves per minute per source using a *Duet* lithotripter (Direx Systems Corporation). The main conclusion was that kidney tissue and function were minimally affected.

The use of low shock wave rates has become a common practice (Yilmaz and Batislam 2010; Schnabel et al. 2015). Nevertheless there are also reports indicating that under certain circumstances the shock wave rate is not as important as believed. An example is a study published by Davenport et al. (2006). The authors compared SWL performed for uncomplicated single renal calculi on 104 patients with a Dornier *Lithotripter S*, using either a 1 or a 2 Hz shock wave delivery rate and found no significant difference in outcome between the two groups. Mazzucchi and colleagues (2010) randomly divided patients with urinary stones into two groups. One group received 3000 shock waves at 1 Hz and the other patients were treated with 4000 shock waves generated at 90 shock waves per minute. The authors defined success as stone-free status or the detection of residual fragments of less than or equal to 3 mm, three months after treatment. Partial fragmentation was defined as significant reduction in the stone size but residual fragments equal to or larger than 3 mm. Their study revealed no significant differences in the stone-free rates between both groups. Furthermore, Nishiyama et al. (2014) performed a study to determine the optimal shock wave rate by analyzing the treatment outcome of 247 patients with ureteral stones, treated at 30, 45, 60, or 80 shock waves per minute using a Dornier *Lithotripter D*. They concluded that stone reduction and clearance at low shock wave rates were similar to those obtained at the higher frequencies.

Ventricular arrhythmia during SWL is not common and in general shock wave delivery rate may be adjusted independently of the patient's heart rate; however, as mentioned above, gated SWL should be used in patients having cardiac arrhythmia or in patients with preexisting premature ventricular complexes (Ganem and Carson 1998).

5.6.6 *Voltage-Stepping and Number of Shock Waves*

Consensus on lithotripter terminology has been an issue for many years (Tolley et al. 1991). The practice of applying standard protocols, using high energy settings and a fixed number of shock waves that is supposed to guarantee stone comminution, should be avoided, because patients may be over-treated. When comparing treatment protocols care should be taken with terms, such as power, voltage, and intensity, because different lithotripters may generate very different pressure waveforms. An inconvenient practice is to express the "dose" given to a patient only in terms of the voltage or intensity setting and the number of shock waves. Voltage settings should only be compared between the same models of lithotripters.

In general it is difficult to determine the moment when the stone is broken to completion. Nowadays, fluoroscopic and ultrasound imaging systems are reliable for stone localization, but in general are not clear enough to determine the treatment endpoint. Acoustic feedback systems to monitor stone comminution are potential solutions (Sect. 5.6.9).

It is known that high peak-positive pressure does not necessarily result in better urinary stone fragmentation (Chuong et al. 1992; Granz and Köhler 1992; Teichman et al. 2000; Eisenmenger 2001). Moreover, high electrical energy may not correlate with high fragmentation power. The energy of the generated shock waves is adjusted by varying the electrical energy stored in the capacitor or set of capacitors of the shock wave source. This is normally done by adjusting the voltage of the power supply; however, the relationship between the voltage of the power supply and the energy of the emitted shock waves is different from one type of shock wave generation mechanism to the other. Even if the shock wave generation mechanism is the same, it could be senseless to only compare voltage settings, because shock wave energy also depends on several other parameters, such as the total capacitance, the electrical impedance, and the design of the shock wave source. The whole pressure waveform, the EFD, and the shape of the focal volume are more important to predict stone fragmentation efficiency than the voltage setting. In the early 1980s when the *HM3* was the only available lithotripter, it was a common practice to report only the voltage adjusted on the shock wave source and the number of released shock waves. As different lithotripter models appeared on the market, other parameters had to be defined to compare between SWL protocols and equipments.

Nowadays, there is a consensus that fragmentation correlates better with acoustic energy than with peak-positive pressure (Granz and Köhler 1992; Eisenmenger 2001). According to many years of experience an $E_{12\text{mm}}$ (Sect. 3.4) between 100 and 130 J is recommended for renal stones and between 150 and 200 J for ureteral calculi (Rassweiler et al. 2011). In an in vitro study, Smith and Zhong (2012) found that it is the averaged pressure incident on a stone and not the absolute peak pressure in the lithotripter field that determines stone fragmentation efficiency.

The so-called *voltage-stepping* or *power-ramping* is recommended both to protect the kidney from tissue damage and to improve stone fragmentation, because stone comminution depends not only on the total acoustic energy, but also on how that

energy is delivered to the stone (McAteer et al. 2003, 2005a). In vitro kidney stone phantom fragmentation revealed that gradually increasing the voltage on the shock wave source enhances stone comminution (Zhou et al. 2004a; Maloney et al. 2006). Furthermore, in vivo experiments confirmed that voltage-stepping could also reduce vascular injury (Evan et al. 2003; Evan and Willis 2007). Demirci and colleagues (2007) evaluated the results of conventional and step-wise SWL in the management of urinary calculi after treating 50 consecutive patients on a *Compact Delta* (Dornier MedTech GmbH) lithotripter. The first group received shock waves generated at 13 kV. In the second group, the treatment protocol consisted of 500 shock waves at 11 kV, 500 at 12 kV, and the rest at 13 kV. The maximum number of shock waves was limited to 3000 in both groups. The success rate 8 weeks after SWL was significantly higher in the step-wise SWL group than in the standard group. Lambert and colleagues (2010) published a prospective randomized trial on 45 patients with stones having a median size of 8 mm, to study the effect of escalating versus fixed voltage on stone comminution and renal injury. Patients were randomized to receive either 2500 shock waves generated at 18 kV on a *DoLi 50* lithotripter (Dornier MedTech GmbH) or a protocol consisting of 500 shock waves at 14 kV, 1000 at 16 kV, and 1000 at 18 kV. To evaluate renal damage, voided urine was analyzed for beta2-microglobulin and microalbumin. About 81 % of the patients in the voltage-stepping group were stone-free one month after treatment. Only 48 % of the patients in the conventionally treated group were stone free. Furthermore, there was a significant difference between microalbumin and beta2-microglobulin 1 week after SWL, suggesting that there seem to be a protective effect against tissue damage when using voltage-stepping.

Nowadays, power stepping protocols are common in SWL (Brown et al. 2014; Schnabel et al. 2015). Only for extremely resistant stones, such as cystine and calcium oxalate monohydrate stones, a high-voltage setting is recommended almost from the beginning of the treatment. In this case, the goal of using high energies from the beginning is to induce cracks in the stone that may get filled with fluid, allowing cavitation to act. The energy should be reduced once the stone has been broken. Interestingly, in vivo studies in pigs suggest that voltage ramping during SWL reduces tissue injury compared with fixed-voltage SWL; however, starting at low or high-voltage produces lesions of similar size (Connors et al. 2009a, b).

The effect of voltage-stepping on treatment outcomes depends on the type of lithotripter and each clinical case. As already shown in Fig. 5.15, for electrohydraulic shock wave sources, the peak-positive pressure increases slowly at voltages above 20 kV (Chitnis 2002). Furthermore, as the electrode tips wear away, the spark-gap increases, causing a pressure change. With some spark-plugs it is advisable to precondition the electrodes by burning them in for about 100 discharges at the lowest voltage setting before starting the treatment (Coleman et al. 1987b; Loske and Prieto 1993).

The proper number of shock waves applied in one SWL session depends on several factors, such as the BMI of the patient, the shock wave source, the stone size, its

composition, and its location. To avoid over-treatment, a general advice is to use a relatively small number of shock waves and keep the intensity setting of the lithotripter low. Good treatment results will be achieved at low total energy and slow shock wave rate if patient selection, stone positioning, voltage-stepping, and shock wave coupling are done carefully. Exposing the kidney to prophylactic shock waves (Sect. 5.6.7) before SWL is an additional advice.

5.6.7 Prophylactic Shock Waves

In 1996 it was reported that shock waves reduce both the glomerular filtration rate (GFR) and renal plasma flow (RPF) in pigs (Willis et al. 1996). A few years later, the same authors showed that RPF did not depend on the voltage setting (using a Dornier *HM3* between 12 and 24 kV) (Willis et al. 2002). Interestingly it was discovered that renal blood flow reduced in both the shock wave-treated and the untreated kidney. This included a bilateral reduction in RPF (Thomas et al. 1988; Eterovic et al. 1999). In vivo experimentation revealed that this phenomenon was mediated by renal nerves and not by circulating vasoconstrictors released by the shock wave-exposed kidney. Delvecchio et al. (2003) performed in vivo shock wave treatments to juvenile female swine and found an increase in free radical activity at sites remote from the treated region. The authors concluded that their observations could be the result of vasoconstriction throughout the treated kidney with resultant ischemia-reperfusion injury. Another surprising effect of SWL on pig kidneys was reported a few years later (Willis et al. 2006). Applying 2000 shock waves generated at a low voltage (12 kV) with an *HM3* lithotripter to one renal pole produced vasoconstriction but no hemorrhagic lesions in a first group of pigs. A second group received 2000 shock waves at 24 kV to one pole and finally, a third group of pigs was exposed to 2000 shock waves at 12 kV to one pole, followed by the same amount of shock waves at 24 kV to the other pole of the same kidney. As expected, important hemorrhagic injury was observed in kidneys treated only in one pole with shock waves generated at a voltage equal to 24 kV; however, kidneys treated at one pole with 2000 shock waves at 12 kV before exposing the other pole to 2000 shock waves produced at 24 kV showed little to no tissue damage. To find the minimum threshold to trigger the abovementioned effect, Willis et al. (2006) tested the use of different amounts of prophylactic shock waves generated at 12 kV. Since similar results were obtained at 100, 500, and 2000 prophylactic shock waves, the authors concluded that the minimum threshold must be below the 12 kV/100 shock wave-setting.

Vasoconstriction induced by the application of low energy shock waves is believed to protect the kidney from subsequent application of high energy shock waves (Handa et al. 2009a). A few years after the initial report describing the prophylactic effect, Connors et al. (2009a) published that the tissue-protecting effect appeared only when the prophylactic treatment was followed by a few minute pause

before starting SWL. Finally, Handa et al. (2012) reported another in vivo experiment with pigs, concluding that renal protection can be achieved without a pause. They demonstrated that the desired protective effect can be obtained following either one of two different methodologies: In the first one, an initial low-pressure shock wave dose is delivered during approximately 4 min before various step-wise SWL protocols and in the second one, a few minute-pause is programmed before starting the SWL. The abovementioned studies, among others, demonstrated that following the appropriate protocol, shock waves can be both harmless to the kidney and efficiently comminute kidney stones. Interestingly, vasoconstriction occurring during SWL has been measured recently in humans (Lee et al. 2015). Nowadays, several lithotripsy centers treat their patients with approximately 100 low energy prophylactic shock waves, followed by a break of a few minutes before starting a standard voltage-stepping SWL protocol.

Motivated by the aforementioned in vivo findings, research to study the phenomena involved in the tissue-protecting effect of low energy shock waves continued. A hypothesis was that the optimum energy level to induce the desired protective effect is lower than the minimum energy setting of a commercial lithotripter. Furthermore, pressure pulses and not necessarily shock waves could be sufficient to protect the kidney tissue before SWL. To expose the kidney to shock waves having a lower energy than those generated at the focal zone using the minimum voltage setting of the lithotripter, prophylactic out-of-focus shock wave exposure was proposed (Loske et al. 2004a). The technique is based on the supposition that the low-energy protective effect may be enhanced if not only a small region, but also a large volume of the kidney is treated with prophylactic pressure waves. During out-of-focus prophylactic pressure wave treatment, the kidney is located at the beam axis of the shock wave generator, but a few centimeters away from the focal spot. Even if during the prophylactic treatment phase the focal spot does not coincide with the stone, no tissue damage is expected, because low energy is used at this stage. Depending on the SSD, the focal spot could be outside the patient's body (Fig. 5.69a). The methodology can be implemented for any lithotripter; however, pressure measurements are recommended to estimate the most convenient location for the kidney during the prophylactic phase. After finishing the prophylactic phase of the treatment, the system is moved so that the kidney stone is at the focal spot as in any standard SWL (Fig. 5.69b). A preliminary in vivo experiment with rabbits revealed that an out-of-focus pressure pulse therapy reduces the shock wave-induced tissue damage to the renal capsule (Fernández et al. 2013). In vivo experiments with pigs could help to path the way towards a clinical application of the out-of-focus therapy. Evan et al. (2008) reported no tissue damage in pig kidneys after clinical doses of shock waves with the wide focal zone, low pressure, electromagnetic lithotripter (Suzhou XiXin Medical Instruments Co., Ltd.) mentioned in Sect. 5.3.4. The lack of injury was attributed to a slow shock wave rate (about 0.5 Hz); however, it is possible that the prophylactic effect also contributed to these results, because a relatively large kidney volume was exposed to low-energy pressure waves (p^+ less than 20 MPa).

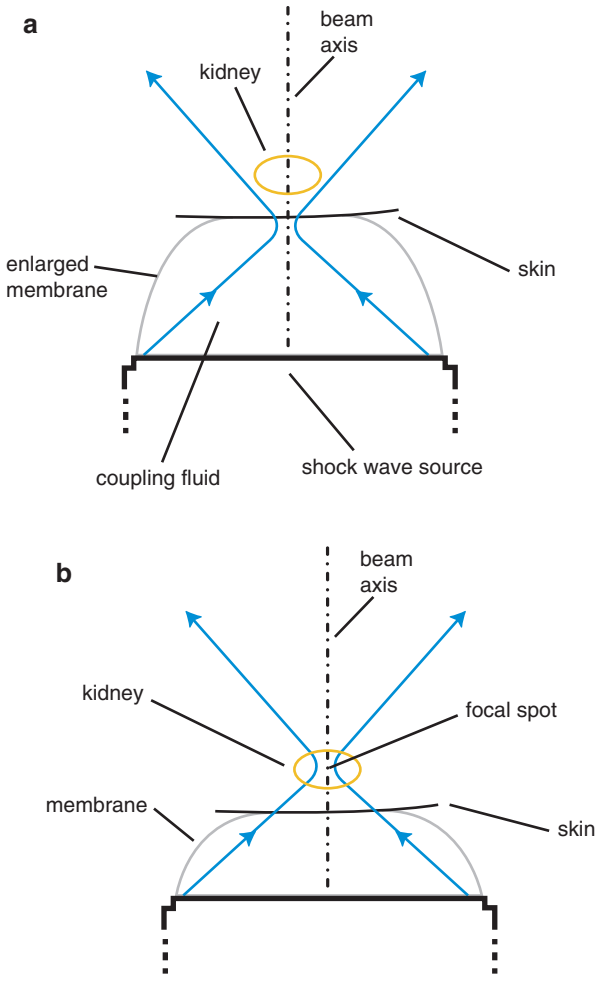


Fig. 5.69 Schematic of pressure wave focusing during (**a**) out-of-focus prophylactic pressure pulse therapy to the kidney and (**b**) shock wave lithotripsy to pulverize a kidney stone

5.6.8 Shock Wave Coupling

Efficient shock wave coupling into the patient is crucial to obtain good results and avoid lesions at the skin. Degassed water is generally used to transmit the shock waves, because it is easy to handle and its acoustic impedance is similar to that of soft human tissue. An additional advantage is that the attenuation of shock waves in water is relatively low. Furthermore, since water is difficult to compress, high pressure amplitudes can be generated at relatively low energy. Degassed water is recommended, because dissolved air and microscopic gas bubbles absorb shock wave energy (Westermark et al. 1998). The peak-positive pressure can be almost two times higher when degassed water is used compared to non-degassed water.

Good coupling was easily achieved with old lithotripters having open water baths, such as the Dornier *HM3* and the Richard Wolf *Piezolith 2300*. As mentioned above, for research purposes, including in vitro and in vivo studies, open-tub shock wave sources are generally easier to use and assure better shock wave coupling than the so-called dry systems (Coleman et al. 1989; Prieto et al. 1991; Loske et al. 2002b, 2003). Modern lithotripters have water-filled cushions to transfer the pressure pulses from the shock wave source into the patient, allowing easy patient positioning and the possibility to treat the patient in prone position (Jenkins and Gillenwater 1988).

Wrinkles of the membrane and the type of gel applied between the coupling cushion and the skin may affect treatment outcomes significantly (Jain and Shah 2007; Bohris 2010). Before starting a treatment it is crucial to remove all air bubbles trapped between the patient's skin and the membrane (Pishchalnikov et al. 2006b; Jain and Shah 2007; Neucks et al. 2008; Bohris et al. 2012). A coupling fluid with low viscosity is suggested, because high viscosity coupling agents may have more air bubbles trapped inside. Good results are normally achieved using warm coupling gel or silicon oil (Fig. 5.70). Air pockets trapped in the gel between the membrane of the water cushion and the patient's skin decrease the fragmentation efficiency significantly (Fig. 5.71). Patients having hair at the shock wave entrance site should be shaved. A 2 % coverage of the water cushion with air pockets can reduce shock wave fragmentation efficiency by up to 40 %. If the SWL treatment is

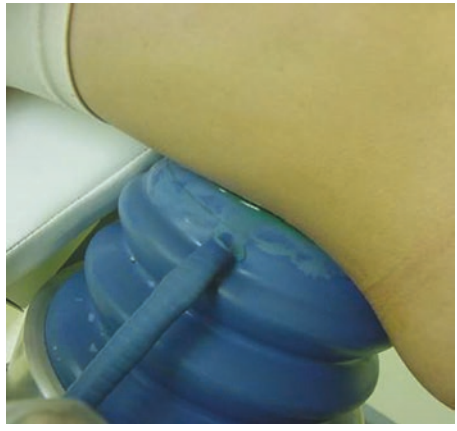


Fig. 5.70 Good shock wave coupling through a water cushion and a warm bubble-free coupling fluid

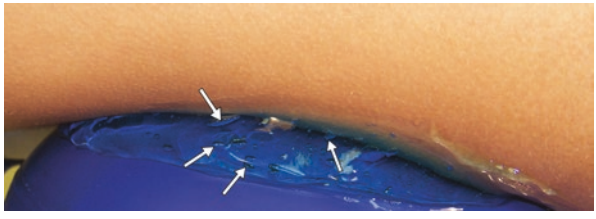


Fig. 5.71 Bad shock wave coupling through a water cushion and a bubbly ultrasound gel. The arrows point at a few air bubbles

interrupted and the patient is moved, the fragmentation efficiency may reduce by more than 80 % (Jain and Shah 2007; Neucks et al. 2008). Bohris et al. (2012) used a camera to evaluate the coupling quality during SWL and found that in more than 60 % of the sessions there was imperfect coupling, accompanied by significant loss of disintegration capability. Tailly and colleagues installed a video camera and an LED light in the shock wave source of a *Gemini* lithotripter (Dornier MedTech GmbH) to visualize and remove all air bubbles before SWL, obtaining efficiency quotients comparable to the control group, but with considerably less shock waves and lower energy level (Tailly 2013b; Tailly and Tailly-Cusse 2014).

During the whole treatment, the patient's skin should be in contact with a sufficiently large area of the water cushion to avoid small air gaps between the membrane and the patient (Figs. 5.72 and 5.73). Bubbles accumulating on the inside of the membrane could also reduce treatment efficiency. A comparative study of the clinical outcomes achieved with the Dornier *HM3* and the tub free *HM4* lithotripters revealed that the results obtained with the *HM3* could only be assured with the *HM4*

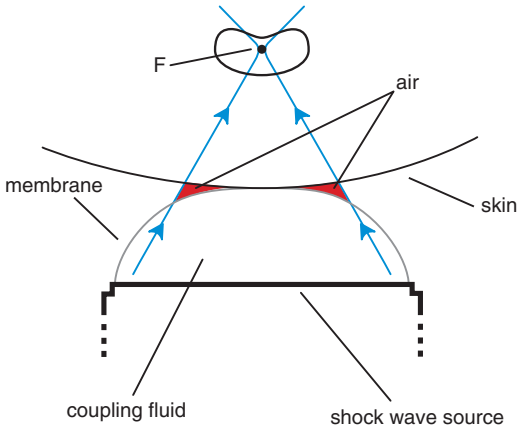


Fig. 5.72 Schematic of poor shock wave coupling during extracorporeal lithotripsy. Air gaps between the membrane and the skin significantly reduce the energy coupled into the patient

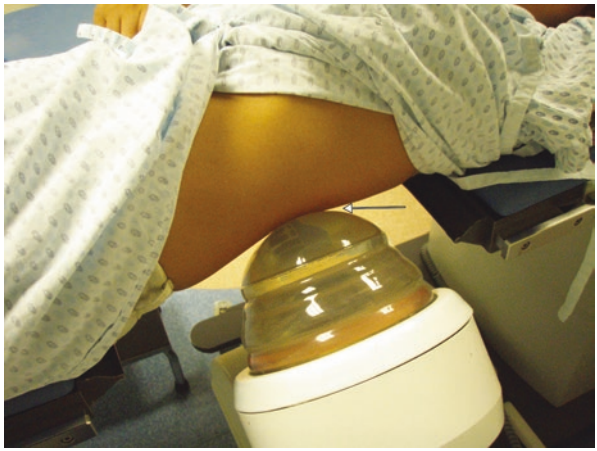


Fig. 5.73 Bad treatment outcomes may be due to small air gaps (*arrow*) between the coupling membrane and the skin

because it had a video camera inside the therapy head to see bubbles trapped inside the water cushion (Jocham et al. 1987). Real-time visualization of the entire coupling interface and a device to remove bubbles from the inner side of the membrane were crucial to avoid excessive shock wave attenuation. In-line ultrasound may also be useful to confirm proper acoustic coupling (Bergsdorf et al. 2008; Neucks et al. 2008); however, ultrasound only detects bubbles in the scanning plane. In order to visualize the entire coupling area, the transducer needs to be rotated.

5.6.9 Imaging Systems and Patient Positioning

Plain abdominal radiographs are still common to detect and follow-up urinary stones; however, for SWL accurate three-dimensional stone localization is essential. Ultrasound with a frequency between 2 and 6 MHz is widely used, having the inherent advantage of real-time imaging without the need of ionizing radiation. Nevertheless, CT has become the method of choice to evaluate stone disease. CT can predict the density of the stone, evaluate the intrarenal anatomy and the SSD. Moreover, urinary stones can be detected either by static or dynamic magnetic resonance imaging (MRI).

Ultrasound real-time imaging of radiolucent stones at a lower cost than fluoroscopy was one of the features of the first piezoelectric lithotripters (Preminger 1989); however, because most ureteral stones are difficult to visualize with ultrasound, today most lithotripters provide imaging with both fluoroscopy and ultrasonography. Changing between imaging modalities allows compensating for the deficiencies of either system. Enhanced resolution, image processing, and combination of imaging modalities have resulted in safer and more efficient shock wave treatments. Automated fluoroscopic localization as in the *Sonoloth i-sys* lithotripter (Fig. 5.25) (EDAP TMS) has resulted in reduced radiation exposure to the patients (Partheymüller 2010). Other examples of modern technology are the tracking system of the *LithoSpace* (Jena Med Tech GmbH), that can be coupled to several models of fluoroscopic or ultrasound imaging devices (Figs. 5.21 and 5.22), and the optical tracking, combined with virtual reality imaging, that assists the operator of the *Modulith* (Storz Medical AG) to position the stone correctly (Wess 2010).

Depending on the design of the lithotripter, the alignment between the shock wave generator and the imaging system should to be verified carefully before starting SWL (Fig. 5.74). Precise system alignment and the use of test equipment to perform in vitro stone fragmentation of well-standardized stone phantoms as recommended by the manufacturer are crucial (Fig. 5.11a). These procedures are generally easy and vary from one lithotripter model to another.

Most lithotripters are equipped with state-of-the-art ultrasound and fluoroscopic imaging systems. Some of them include in-line use of imaging systems. Selecting the most convenient acoustic window to guarantee that no bony structures and air cavities interfere the shock wave path is essential. Some lithotripters with isocentric

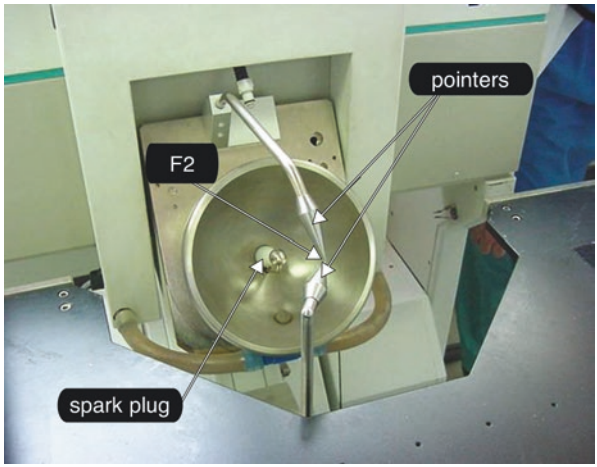


Fig. 5.74 Photograph showing the shock wave generator of a *Tripter Compact* lithotripter (Direx Systems Corporation, Canton MA, USA) before aligning the shock wave generator and the imaging system.

design and a movable shock wave source facilitate this task allowing treatments in over- and undertable modalities.

Fluoroscopy is excellent to target radiopaque stones in the upper urinary tract. An advantage of fluoroscopy compared to ultrasound is the possibility of in situ treatment of ureteral stones along the whole ureter. Main disadvantages are that small stones may be difficult to locate and that no real-time follow-up is possible, even if nowadays pulse-progressive fluoroscopy minimizes radiation exposure. For radiolucent stones, intravenous contrast agents (dyes) are used. Retrograde instillation of contrast, using a ureteral catheter (retrograde pyelography) is also helpful. An important advice to significantly reduce the radiation to the patient is to use the collimators to obtain a small fluoroscopic window once the stone has been identified (Tiselius and Chaussy 2012).

Ultrasound visualization before and during SWL is recommended whenever possible (Chaussy et al. 2014). In general, ultrasonography has the advantage of real-time imaging of radiopaque and radiolucent renal stones. Some lithotripters are equipped with an in-line ultrasound scanner which is generally useful to separate between multiple stones. In-line ultrasound also allows easier targeting of proximal and distal ureteral stones in the path of the shock waves. Real-time coaxial ultrasound is a good method to assure reliable stone localization for lithotripters with narrow focal zones. As shown in Fig. 5.75, in-line ultrasound imaging reliably detects lateral and diagonal deviations of the stone. The same figure reveals that, even if axial deviation cannot be corrected by using only in-line systems, this may not be critical, because focal zones are cigar-shaped. If the stone is slightly displaced along the beam axis, the shift will not appear on the screen; however, the stone may still be inside the focal volume. A further advantage is that in-line ultrasound can also be used to confirm shock wave coupling quality. However, it should always be considered that ultrasound and shock waves do not follow exactly the same path through the various tissues. This could produce slight positioning errors

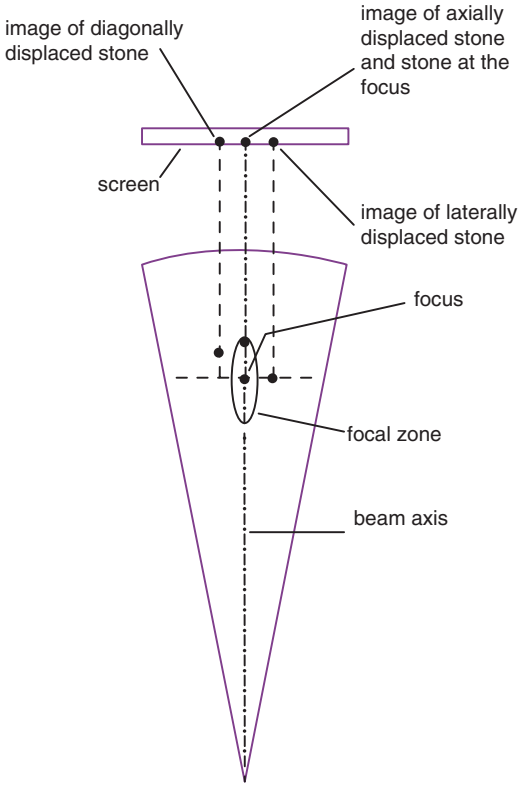


Fig. 5.75 In-line ultrasound imaging systems reveal whether the stone is shifted laterally or diagonally; however, axially displaced stones may appear as being at the focus. All points located along the beam axis are projected as the same spot on the screen

(Wess et al. 1995). Furthermore in-line ultrasound images may include artifacts caused by the coupling interface. Off-line ultrasound scanning generally has better image qualities, allowing the operator to choose the best acoustic window and providing a good appraisal of the fragmentation process. This image modality detects axial deviation; however, to detect diagonal deviation, two projection angles may be needed (Fig. 5.76).

A disadvantage of ultrasound is that the learning period is relatively long and reliable images are obtained only if the stones are located inside the kidney or in the proximal and distal section of the ureters. Achieving good ultrasound image quality and finding suitable acoustic windows using the lithotripter system is generally more complicated than with hand-held ultrasound scanners.

Ultrasound imaging may affect the measured stone size. This may lead to inconvenient treatment protocols. To address this problem, Dunmire et al. (2015) developed a computerized kidney stone-sizing program to outline the stone width based on a grayscale intensity threshold. The purpose of their work was to reduce overestimations when imaging kidney stones. The system was tested in an in vitro bath model. Images obtained with a commercial equipment were compared with those of the software-based research device. With the standard system, overestimation

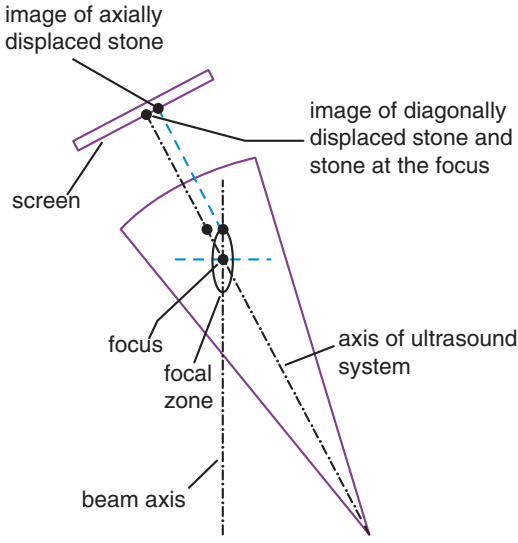


Fig. 5.76 Off-line ultrasound imaging systems reveal axial displacements; however, diagonally displaced stones may appear as being at the focus

increased with both gain and depth. Overestimation was reduced and did not vary with depth, using the research device. The same group investigated the acoustic shadow width as an alternative measure of stone size (Dunmire et al. 2016). Accuracy was significantly improved by measuring the ultrasound shadow of the stone in an in vitro bath model.

Because of patient breathing, stones can move 50 mm or more during SWL. If the focal zone of a shock wave source is large, the stone is more likely to receive more energy than it would with a small focal zone. The effect of stone motion on in vitro comminution efficiency was studied by Cleveland et al. (2004). The authors reported that depending on the respiratory rate, the length of stone movement, and the size of the focal volume, the stone may be outside the focal zone during 50 % of the treatment. Similar results have been obtained in patients. Real-time ultrasound imaging revealed that approximately 40 % of shock waves miss the stone during one SWL session, primarily from movement with respiration (Sorensen et al. 2012). A partial solution to breathing movement is to position the patient so that the focal spot coincides with the stone at the moment of expiration, reducing the number of shock waves released during the time that the stone is out of focus (Tiselius and Chaussy 2012). A proper analgesia regimen may also increase the hit rate by reducing the patient's respiratory movements. Some lithotripters such as the Siemens *Lithostar* offered respiratory gating shock wave emission; however, the system was not popular because treatment time increased considerably. As mentioned above, abdominal compression belts also reduce stone movement due to respiration (Honey et al. 1992; Argyropoulos and Tolley 2007; Tiselius and Chaussy 2012). Furthermore, high-frequency ventilatory respiration anesthesia has been successfully used in the past to reduce stone movement. It was abandoned by most urologists, because of its invasiveness and potential negative effects on patient oxygenation.

Ultrasound stone tracking is another interesting approach to improve the hit rate and avoid over-treatment during SWL. A challenge of this technique is that the stone moves in three dimensions while ultrasound offers two-dimensional images. Thomas et al. (1996) applied the time reversal process to track a moving stone and studied the possibility to use a piezoelectric shock wave generator in which the focal spot follows the stone during SWL. Ultrasound based real-time stone tracking for treatment monitoring, adjustment of the shock wave source position according to the movement of the stone and shock wave trigger control have been developed by several groups to improve accuracy (Orkisz et al. 1998; Chang et al. 2001, 2002, 2013; Chen et al. 2009).

Acoustic feedback systems use a receiver that registers the pressure waves reflected off the stone fragments. The technique can be used both to target stones and to evaluate stone fragmentation. In principle it is possible to discriminate between large and small particles because the resonance frequency of an elastic object is inversely proportional to its size, i.e., smaller fragments generate signals with higher frequencies. Owen and colleagues (2004) developed an acoustic feedback system to improve in vitro stone fracture by gating shock wave emission with targeting, taking advantage of the fact that in-focus and out-of-focus acoustic emissions are different from each other. The same group developed a system to detect resonant scattering from kidney stone models to distinguish fractured stones from intact stones (Owen et al. 2007). Bohris et al. (2003) demonstrated that a spectral Doppler signal can be an excellent tool for hit/miss monitoring in SWL. Leighton and co-workers (2008) adapted a sensor on the patient's skin to passively monitor acoustic signals that propagate through the body after each lithotripter shock wave. The system predicted treatment outcome in 95 % of clinical cases.

Excellent results can be obtained with most extracorporeal shock wave lithotripters if patient selection and patient positioning is done carefully. Informing the patients about the basics of SWL before starting the treatment reduces their anxiety and may contribute to achieve good results. Patient positioning should be confirmed several times during SWL and always guarantee shock wave passage without interference with skeletal structures or bowel gas.

It is well known that fragmentation efficiency drops drastically when moving away from the focal spot in a direction perpendicular to the beam axis of the shock wave source (Chitnis 2002). This obviously depends on the design of the shock wave source; however, an error along the focal axis always influences the fragmentation efficiency less than shifting the stone the same distance from F in another direction. Figure 5.77 shows that a kidney stone model (diameter 10 mm) placed at the second focus of an electrohydraulic shock wave source is severely damaged after 300 shock waves, while a stone 10 mm off-axis is almost intact. Similar fragmentation as in *F2* was achieved with the same lithotripter by placing the stone along the focal axis up to 40 mm away from *F2*.

Wide-focus shock wave sources allow a high positioning flexibility and there might be no significant differences in clinical outcomes between using intravenous sedation and general anesthesia. This was confirmed for non-staghorn upper urinary tract stones by Zommick and colleagues (1996). When using a lithotripter with a

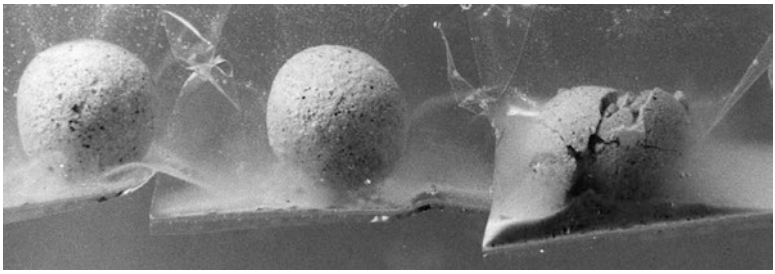


Fig. 5.77 Photograph of three kidney stone phantoms immersed in water, after exposure to 300 shock waves in a research electrohydraulic shock wave generator. The stone on the right side was centered at the focal spot. The other two stones were separated approximately 10 mm from each other

small focal zone, some authors suggest to sedate the patient (Eichel et al. 2001; Sorensen et al. 2002).

Because the bony pelvis prevents shock wave transmission, distal ureteric stones have been treated with the patient in prone position, instead of in supine position, as is common for SWL of renal and upper ureteric stones. Lithotripters designed to couple the therapy head both above and under the treatment table, allow patients to be treated in a supine position for ureteral stones at all levels of the urinary tract. Another possibility, especially for patients where treatment in the prone position is not possible, is the use of a transgluteal approach to the distal ureter (Leveillee et al. 1994; Lu et al. 2010; Sun et al. 2010; Istanbulluoglu et al. 2011). In this case, shock waves are delivered via the gluteus maximus muscle, and propagate via the greater sciatic foramen to the distal ureter. Phipps et al. (2013) compared SWL for distal ureteric stones treated by the prone and transgluteal approaches using a *Sonolith Vision* lithotripter (EDAP TMS). The proportions of patients who were stone-free after one session within the prone and transgluteal treatment groups were 40 and 78 %, respectively. This seems to be reasonable, because in the prone approach, shock waves may be blocked by bowel gas.

5.6.10 Computed Tomography Attenuation Numbers

The prediction of treatment outcomes and an appropriate decision-making are important to prevent unsuccessful SWL; however, accurate predictions are not easy to do since even under well controlled in vitro conditions, fragmentation coefficients vary greatly after exposure to the same dose of shock waves (Williams et al. 2003). Advances in imaging have resulted in useful determinations for SWL, such as the stone size and the CT attenuation value (Springhart and Preminger 2004). The CT attenuation value or CT attenuation number is a normalized value of the X-ray absorption coefficient, i.e., a measure of radiodensity used to evaluate computed axial tomography images. Because CT scanners are calibrated with reference

to water, CT attenuation values belong to a scale in which the radiodensity of distilled water at standard temperature and pressure (STP) is defined as zero and that of air at STP is defined as −1000. The CT attenuation number is obtained according to the following equation:

$$\text{CT attenuation number} = 1000 \times \frac{\mu - \mu_w}{\mu_w - \mu_a}, \tag{5.1}$$

where μ is the average linear attenuation coefficient of a voxel and μ_w and μ_a are the linear attenuation coefficients of water and air, respectively. According to this definition, CT numbers can have negative values. CT attenuation numbers are often reported in Hounsfield units (HU), even if the attenuation value actually has no units. The attenuation number for fat is between approximately −120 and −60 HU, the value for soft tissue is between −300 and −100 HU, and for dense bone the attenuation number is about 3000 HU.

As already mentioned, treatment outcomes depend on several parameters, such as the type of lithotripter used, the stone composition, size, internal structure, location and the medium surrounding the calculus. From the beginning of SWL it was known that highly radiopaque stones were more difficult to pulverize than less radiopaque stones. The results of 123 SWL treatments on a modified *HM3* lithotripter were correlated to several pretherapeutically identified parameters by Mattelaer and colleagues (1994). Stone size, radiopacity and grade of dilatation of the upper urinary tract had a direct correlation to treatment outcome. Bon et al. (1996) searched for radiographic prognostic criteria for SWL with a *Sonolith 3000* lithotripter, finding that less dense and rough calculi achieved a SFR of about 79 %, while dense and smooth calculi had a SFR of approximately 34 %. Their suggestion was that patients with dense, smooth calculi located in the lower calyx and larger than 15 mm should not be treated by SWL. Dretler and Polykoff (1996) compared the crystallographic composition of calcium oxalate stones with information obtained from plain radiographs to predict their fragility. Their main conclusion was that smooth and very radiodense stones are generally composed of calcium oxalate monohydrate and are very resistant to SWL.

Favela et al. (2005) studied the correlation between CT numbers and in vitro fragmentation of kidney stone phantoms by shock waves, concluding that the fragmentation coefficient of a stone, as defined in Sect. 5.6.12, can be obtained from the initial stone weight W_i (in g) and the CT attenuation number (CTN) by using the following equation:

$$FC = 90.63 - 6.46W_i - 0.034\text{CTN}. \tag{5.2}$$

As an example, the *FC* of a 0.5 g stone having a radiological density of 100 HU is approximately 84 %. A stone with same weight but 1000 HU-density has a *FC* equal to 53 %. Increasing the stone weight three times, reduces the fragmentation coefficients to approximately 78 % and 47 % for CT values of 100 and 1000 HU, respectively. In order to evaluate if a similar behavior could be observed in vivo,

SWL was performed to pigs with previously implanted artificial kidney stones (Hurtado et al. 2007). According to the in vitro findings, the in vivo results showed that a poor outcome may be expected after SWL of large stones having a high radiodensity. An in vitro study by García Marchiñena et al. (2009) revealed that SWL success increases significantly if stones have a density lower than 1000 HU. Cleveland and colleagues (2001) demonstrated that the initiation of micro-fractures within kidney stones treated in vitro by shock waves can be detected by micro-computerized tomography.

CT is safe, fast and has a very high accuracy in the diagnosis of urolithiasis (Dalrymple et al. 1998). It has been used to identify the chemical composition of urinary calculi and to visualize their internal structure (Mitcheson et al. 1983; Mostafavi et al. 1998; Williams et al. 2001). Micro-computerized tomography may also help to identify the mineral composition of urinary stones non-destructively (Zarse et al. 2004a, b). Non-contrast computed tomography (NCCT) is capable of producing thin-slice images. Stone size, shape and attenuation values can be measured easily. Dual-energy CT (DECT) further improved the characterization of anatomic structures. Using post-image acquisition data processing, it has been demonstrated that DECT allows for accurate in vitro (Ferrandino et al. 2010) and in vivo (Zilberman et al. 2010) discrimination among several types of urinary calculi.

Many authors reported that analyzing the shape, structure and density of a stone by CT may be a guide for pre-treatment decisions (Dretler and Spencer 2001; Pareek et al. 2003, 2005a; Williams et al. 2004; Hurtado et al. 2007; Kacker et al. 2008; Ouzaid et al. 2012; Vivaldi et al. 2011; Abdelaziz et al. 2014; Cakiroglu et al. 2014; Nakasato et al. 2015); however, data should be analyzed carefully, because results depend on image resolution. If the resolution of the CT scanner is low, the mean attenuation value is affected by volume averaging with the surroundings, i.e., as the stone gets smaller, error in CT-density determination raises. Small stones with low CT value can be overlooked on helical CT (Saw et al. 2000b). Furthermore, radiological density values also depend on X-ray energy, location of the stones inside the scanner, slice thickness, and calibration of the equipment (Williams Jr et al. 2007; Stewart et al. 2015).

Krishnamurthy et al. (2005) published the results of 211 patients treated with SWL for solitary renal pelvic stones (less than or equal to 20 mm). Using the pre-operative kidney, ureter, bladder (KUB) plain frontal supine radiograph, radiodensities were determined to be either less than, equal to, or greater than the density of the ipsilateral 12th rib. The SFR was determined at 3 months by KUB plain X-rays. The authors concluded that pre-operative KUB radiograph radiodensities do not predict lithotripsy treatment outcome for stones smaller or equal to 10 mm within the renal pelvis. They also mention that for stones larger than 10 mm, radiodensity may be useful to select the appropriate therapy in conjunction with other stone parameters.

Saw and coworkers (2000a) found an inverse relationship of the mean HU of urinary stones to the stone-free rate after SWL. They also reported that the correlation of CT attenuation with fragmentation efficiency disappeared when scanning was performed at one-millimeter collimation. In a prospective study, other authors analyzed the attenuation values of renal calculi (up to 20 mm in diameter) of 30 patients,

obtained with unenhanced axial CT. Their main conclusion was that the success rate was significantly lower for stones with an attenuation value higher than 1000 HU, compared to stones with a density of less than 1000 HU (Joseph et al. 2002). Singh et al. (2004) also reported that stones with CT values smaller than 1000 HU had significantly higher success rates compared to those with values above 1000 HU.

Gupta et al. (2005) analyzed the usefulness of NCCT density in determining the fragility and clearance of calculi in patients treated with SWL. Measuring the treatment outcome in terms of fragmentation and stone fragment clearance, they concluded that patients having calculi with a density larger than 750 HU had a more than ten times greater probability of needing three or more SWL sessions than patients with attenuation values below 750 HU. Furthermore, they concluded that according to their analysis the attenuation value had a greater impact on SWL outcome than the size of the stone. El-Nahas et al. (2007) evaluated the value of NCCT as a possible predictor of successful SWL performing NCCT on 120 consecutive patients with a 5–25 mm solitary renal stone. Stone attenuation values were measured using a bone window. SWL failure, defined as no stone fragmentation after three sessions, was observed in 15 patients. Attenuation values higher than 1000 HU and the BMI resulted to be the significant independent predictors of failure.

Perks et al. (2008) performed a retrospective study using the database from SWL to 111 patients that had a solitary 5–20 mm renal stone. Calculus location, size, CT attenuation value, and SSD were determined on NCCT before shock wave treatment. According to their findings, a stone attenuation lower than 900 HU, an SSD shorter than 90 mm, and the stone composition predict for treatment success. These results were independent of stone location, size and BMI. Nakasato and colleagues (2015) also performed a retrospective study and determined the HU of renal and ureteral stones from 260 patients who underwent SWL to evaluate the reliability of HU to predict treatment success as well as stone composition. A multivariate analysis revealed that both stone location and mean HU were predictors of SWL outcome. Success rates were significantly higher for stones having a density lower than 815 HU compared to stones with more than 815 HU. Using the density values it was not possible to differentiate between calcium oxalate monohydrate and calcium oxalate dihydrate stones; however, HU of calcium oxalate and calcium phosphate stones were higher than those of uric acid stones.

After a prospective study, Shah et al. (2010a) reported that the EQ (Sect. 5.6.12) of SWL for upper urinary tract stones was significantly better for stones with an attenuation value of less than 1200 HU. The number and intensity of shock waves required to comminute stones with low attenuation value was also significantly lower. Nevertheless, the stone-free rates between both groups (more than and less than 120 HU) was not statistically different.

Abdelaziz et al. (2014) determined the role of stone density and SSD in predicting the success of approximately 90 patients who received SWL for renal and upper ureteric stones. The authors concluded that stone densities lower than 500 HU are highly likely to result in successful treatments, while SWL to patients having stones with a density above 800 HU is unlikely to be successful. No statistically significant differences in mean SSD between successful and failure groups could be found.

Data from 144 patients, who underwent SWL for ureteral stones, were retrospectively reviewed by Cakiroglu and colleagues (2014). Stone densities were classified into three groups: smaller than 500 HU, between 500 and 1000 HU and above 1000 HU. The sizes of the calculi were divided into smaller than 10 mm and larger than 10 mm. SWL failure was defined as any fragments remaining within the ureter. The results showed that the group with the highest radiodensities was significantly different from the other two groups. No meaningful differences were observed between the 500–1000 HU-group and the group consisting of patients having stones with a density less than 500 H. The main conclusion of this analysis was that although stone density predicted the failure of SWL, the size of the stone is a more important criterion for successful lithotripsy of ureteral stones.

According to most publications it seems reasonable to believe that a density value as detected by NCCT above 1000 HU is a predictor of failure to fragment stones by shock waves, especially in obese patients. Nevertheless, there are also reports indicating that CT attenuation does not predict stone composition and that there is a poor correlation between CT values and fragmentation after SWL (Motley et al. 2001). Erdogru et al. (2005) reported that radiodensity did not predict SWL outcome for solitary stones (smaller or equal to 20 mm) located in the renal collecting system. Other groups such as Aeberli and colleagues (2001) could not detect a correlation between stone radiodensity and disintegration after SWL with a Dornier *HM3* lithotripter. Using a 1.25 mm imaging slice, Zarse et al. (2007) found that HU values did not correlate with resistance to SWL in calcium oxalate monohydrate stones.

Fortunately, CT technology is rapidly improving and higher spatial resolution and scan speed will soon be available. Nowadays, multi-detector helical CT with isotropic imaging and three-dimensional image reconstruction provide helpful information and may be used as a tool to predict whether a given stone is amenable to fragmentation by SWL. Nevertheless, it is important to keep in mind that SWL outcome is also highly dependent on the lithotripter and the operator.

5.6.11 Stone Size, Composition and Location

The probability of success decreases as stone size increases. Generally SWL is not recommended for stones larger than 20 mm (Sorensen and Chandhoke 2002; Abdel-Khalek et al. 2004; Al-Ansari et al. 2006). For bigger stones, the need for re-treatment and adjunctive therapy increases. To secure drainage, pre-SWL stenting could be helpful in patients with large stones. For patients with small stones, a high success rate can be achieved in renal and ureteral stones with and without previous ureteral stent placement (Pryor and Jenkins 1990; El-Assmy et al. 2006b; Seitz et al. 2009). Since treatment outcome strongly depends on stone size, volume determinations using NCCT have been suggested as independent predictors of success for SWL of upper urinary tract calculi (Bandi et al. 2009).

It is well known that uric acid stones, calcium oxalate dehydrate and magnesium ammonium phosphate stones are susceptible to shock waves; however, calcium

oxalate monohydrate, calcium cystine or brushite (calcium monohydrogen phosphate) calculi are difficult to break (Chuong et al. 1993). Smaller stones and those with a coarser crystal structure pulverize more easily (Bhatta et al. 1989). Kim et al. (2007) also confirmed that rough cystine stones break more easily. Brushite stones are hard, making them resistant to deformation, fracture propagation and cavitation-induced microjets (Zhong and Preminger 1994). Unfortunately, knowing the composition of a stone is not enough for a reliable prediction, because stone fragility varies a lot within stones having a uniform composition.

For lower pole stones the SFR after SWL is relatively low. Renal anatomy and gravity are responsible for the retention of stone debris. Regardless of this, SWL normally yields better outcomes in patients with smaller stone burdens. If the patient has diverticula caused by infundibular stenosis, the stone debris may not pass the obstruction and invasive techniques are recommended. Techniques, such as mechanical percussion inversion may help passage of lower pole stone fragments after SWL (D'A Honey et al. 2000; Pace et al. 2001). A randomized controlled study of mechanical percussion, diuresis, and inversion (PDI) therapy to assist passage of lower pole renal calculi after SWL published by Chiong et al. (2005) revealed that a significant higher SFR was achieved for patients that received PDI therapy after SWL compared to SWL therapy alone.

Clinical practice has shown that SWL is more efficient to fragment proximal stones than mid or distal ureteral stones. Ringdén and Tiselius (2007) defined a "hardness" factor in terms of the number of SWL sessions, the number of shock waves and the voltage settings on the shock wave source and calculated this factor for different stone compositions using the records of 2100 patients. Their results revealed that cystine and brushite stones had the highest factors (2.4 and 2.2, respectively).

An interesting scoring system, referred to as *Triple D Score* was published by Tran et al. (2015). Their score, based on *receiver operator characteristic curves*, i.e., plots of the true positive rate against the false positive rate for different cut-points of a diagnostic test, accurately predicts SFR. It is simple to obtain and can be reported by radiologists. The authors used data from a large group of SWL-treated patients to generate plots of cut-off values of stone density, SSD, ellipsoid stone volume, and SFR. The score was obtained based upon the number of cut-off values a stone fell below.

5.6.12 Efficiency Evaluation

Reports on clinical SWL outcomes are numerous; however, direct comparison between independently published results is generally difficult and sometimes even senseless, because variable practice patterns, protocols and definitions are used.

The performance of a lithotripter can be evaluated from different points of view and several criteria have been adopted by different authors and manufacturers, sometimes to highlight the features of a specific model. Evaluations include recording of the pressure field according to the IEC 61846 international standard to determine

the −6 dB, 5 MPa and 10 MPa focal zone (Sect. 3.4), the EFD (Sect. 3.5), the in vitro fragmentation coefficient of standardized stone phantoms, the shape and size of craters produced in vitro to stone phantoms (Fig. 4.5), as well as high-speed recording of acoustic cavitation generated near the focal spot. Evaluation of shock wave focusing, patient positioning techniques, and the quality of the imaging systems of a lithotripter are also crucial.

Shock wave sources for SWL are easier to evaluate than ESWT systems. Since extracorporeal shock wave lithotripters are designed to pulverize calculi, in vitro fragmentation of stone phantoms having different physical properties provide valuable information of their performance (Heimbach et al. 2000; Teichman et al. 2000; Chitnis 2002; van Cauwelaert 2004; McAteer et al. 2005b). These tests are good scenarios, where the variability of one calculus to the other is negligible, and the changes associated to the patient's anatomy, different treatment protocols and the skills of the lithotripter operator do not interfere. Nevertheless, they should not be used as the only parameter to evaluate extracorporeal lithotripters. Shock wave sources having a narrow focal zone can be excellent to comminute stones in vitro; however, their clinical efficiency will depend on the imaging systems, the skills of the operator and the specific protocol used.

A common way to evaluate the in vitro fragmentation of a lithotripter is by obtaining its *fragmentation coefficient*, defined as

$$FC = \frac{100\left(W_i - W_f\right)}{W_i}, \tag{5.3}$$

where W_i is the initial intact stone weight and W_f is the weight of fragments larger than 2 mm.

Because urologists are interested in stone-free rates various SWL *efficiency quotients* have been proposed. A popular efficiency quotient (EQ) was defined as (Denstedt et al. 1990; Rassweiler et al. 2001):

$$\mathrm{EQ} = \frac{\%SFP}{100\% + \%RT + \%PAP} \times 100, \tag{5.4}$$

where $\%SFP$ is the percentage of stone-free patients, $\%RT$ is the percentage of re-treatments, and $\%PAP$ is the percentage of post-SWL auxiliary procedures needed.

Since this efficiency quotient does not consider all auxiliary methods, a so-called *extended* EQ, that considers both pre- and post-lithotripsy procedures, was defined (Rassweiler et al. 1992, 2001, 2005; Tailly et al. 2008):

$$\text{Extended EQ} = \frac{\%SFP}{100\% + \%RT + \%PPAP} \times 100, \tag{5.5}$$

where $\%PPAP$ stands for pre- and post-SWL auxiliary procedures. Extended EQ values have been reported to vary from approximately 25–80 (Tailly 2010). A further

EQ, the *modified* EQ, makes a distinction between adjuvant and therapeutic post-shock wave treatment procedures (Rassweiler et al. 1992, 2001, 2005):

$$\text{Modified EQ} = \frac{\%SFP - \%CAM}{100\% + \%RT + \%PPAP} \times 100, \tag{5.6}$$

where *%CAM* stands for the percentage of curative auxiliary methods. Some authors express the efficiency quotients without multiplying by 100.

These efficiency quotients do not depend only on the quality and design of the lithotripter but also on the skills and experience of the staff, the treatment protocol (patient selection, stone size, shape, composition, etcetera), as well as on the hospital management and facilities. EQ values should be used to evaluate the efficiency of a therapy service as a whole, and not as the only measure to compare lithotripters. This is evident when looking at a comparison of the extended EQs (Tailly 2010) of 11 SWL reports, all using the non-modified Dornier *HM3* lithotripter. Results show that the lowest value (EQ = 25) was published 9 years after (Frick et al. 1998) the highest value (EQ = 67) (Lingeman et al. 1989). Another example is an EQ of 31 (Bierkens et al. 1992) compared to an EQ of 59 (Rodrigues Netto et al. 1992), obtained both with a Siemens *Lithostar*.

5.6.13 Final Comments and Recommendations

Many hospitals benefit from a multifunctional lithotripter with easy-to-use software to document treatment settings, a radiotranslucent patient treatment table with good accessibility, high load capacity and Trendelenburg positions, i.e., supine positions on the treatment table, so that the pelvis of the patient is higher than the head. As mentioned before, when choosing a lithotripter it should be remembered that voltage or intensity settings do not mean "power" or "capacity" to comminute urinary stones. The energy density of the shock wave source, the total energy at the focal volume, the sizes of the focal zones and the pressure distribution should be considered. Under certain circumstances, a disadvantage of large aperture shock wave sources can be a reduction of shock wave energy caused by interference with pelvic bones and spine (Tiselius and Chaussy 2012). As shown in Fig. 5.78, the risk of shock wave obstruction is higher with large aperture shock wave generators. Furthermore, the deeper in the body a stone is located, the more important it is to identify possible structures in the shock wave path (Tiselius 2013b).

SWL may be painful. Nevertheless, there exists no standardized protocol for pain control. Treatments can be managed without anesthesia, with local anesthesia or intravenous sedation (Tiselius and Chaussy 2012). Opioids, in combination with sedatives are classical for pain control during SWL. Subcutaneous infiltration with local anesthetics and dermal anesthesia are also used. Improved treatment outcomes have been reported using general anesthesia (Eichel et al. 2001; Sorensen et al. 2002); however, general anesthesia and spinal anesthesia are used mainly to treat

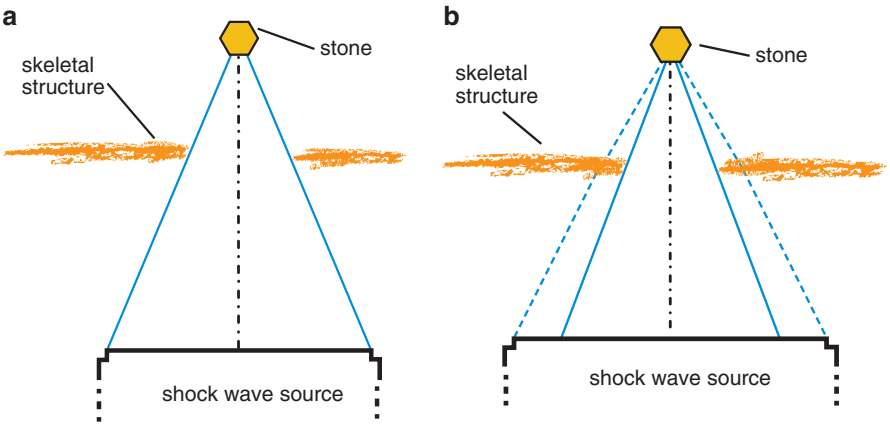


Fig. 5.78 Shock wave focusing close to a skeletal structure with (**a**) a small aperture and (**b**) a large aperture shock wave source. Skeletal structures may absorb a significant percentage of the shock wave energy. (Adapted from Tiselius and Chaussy 2012)

children. An alternative is inhalational anesthesia because it provides the advantage of a fast recovery. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also recommended. Some authors have suggested patient-controlled analgesia (PCA) to achieve more accurate pain control (Schelling et al. 1996; Chin et al. 1997; Alhashemi and Kaki 2006). Specific analgesic regimes may contribute to this (Kumar et al. 2007). Tailly et al. (2001) reported that intravenous administration of a combination of alfentanil and propofol via a PCA device is a reliable and safe method of analgesosedation for SWL. According to their experience, patient satisfaction was high, and side effects were uncommon. Other groups have reported that both acupuncture and electroacupuncture are effective analgesia for patients undergoing SWL (Wang et al. 1994; Chang et al. 2000; Rogenhofer et al. 2004; Chen et al. 2014). Ozkan et al. (2012) compared three different analgesic protocols during SWL and concluded that additional administration of analgesics was decreased with intravenous lornoxicam in comparison with paracetamol and only tramadol.

Thorough information on drugs for pain management in SWL can be found in an article published by Bach et al. (2011). Pain control will depend on the lithotripter model, the EFD, the SSD, the shock wave entrance site and several case-related factors. In general young female patients, as well as depressed or anxious patients experience more pain during SWL (Chaussy et al. 2014). This increases the risk that the patient moves or intensifies the respiratory motion. Furthermore, it could raise the patient's blood pressure, which may increase the risk of hematoma formation. General anesthesia is recommended in extremely anxious patients.

The use of pre-SWL antibiotics is required in patients with infection-related stones or in cases of positive urine culture results. After SWL, stone fragments may remain in the renal collecting system for a long time and attenuate the effects of antibiotics used against infecting bacteria living inside them (Sect. 7.7). Because of

this, eradication of all infected fragments, instead of prolonged use of antibiotics is important for the clearance of infection (Riad et al. 2008).

There is evidence indicating that medical expulsive therapy (MET) facilitates ureteral stone passage after SWL for urolithiasis (Seitz 2010). Administration of an α-blocker or a calcium channel blocker associated with non-steroidal anti-inflammatory drugs (NSAIDs) has been reported to be helpful to clear stone fragments (upper, middle or lower ureteral stones with sizes between 4 and 14 mm) after SWL (Micali et al. 2007; Losek and Mauro 2008; Park et al. 2013), for treating Steinstrasse in the lower ureter after SWL, and after treating renal stones with a size between 4 and 20 mm. *Steinstrasse* ("street of stones" in German) refers to the presence of multiple stone fragments lined up in the ureter leading to obstruction.

MET as adjuvant therapy after SWL for ureteral calculi has beneficial effects (increased SFR, short expulsion time, less pain), and is supported by the European Association of Urology (EAU) (Türk et al. 2015) and the American Urological Association (AUA). The role of alfa-blockers on ureteric stones as MET has been recently questioned in a large multi-center doubled blind randomized trial (Pickard et al. 2015); however, further research is needed.

The environment surrounding a stone influences stone fragmentation during SWL. Stones trapped inside a major calix commonly have a fluid-filled expansion chamber, facilitating cavitation-induced stone comminution; however, ureteral stones may have only a small part of their surface exposed to fluid, reducing the influence of cavitation on the fragmentation process. Retrograde infusion of a convenient fluid might enhance SWL outcome. In vivo experiments performed by Bailey and colleagues (2005) suggested that introducing X-ray contrast agent through a ureteral catheter could enhance cavitation and improve stone comminution. Furthermore, ex vivo manufactured microbubbles, equipped with bisphosphonates that specifically attach to the hydroxyapatite crystals observed in most kidney stones, have been proposed by Ramaswamy et al. (2015) as an aid in diagnostics and lithotripsy. The microbubbles could be injected into the collecting system and acoustic energy (not necessarily shock waves) could be applied once the bubbles are attached at the stone surface. The microbubbles would enhance cavitation and stone fragmentation. Collateral tissue damage is expected to be reduced, because these bubbles would preferentially bind to the stone and not to tissue.

Because most patients undergoing emergency SWL have dilation of the ureter and the renal pelvis, producing a natural expansion chamber, high success rates have been reported with obstructive ureteral stones (Baert and Willemen 1990; Cass 1992; Numa et al. 1994; Doublet et al. 1997; Joshi et al. 1999; González et al. 2000; Tligui et al. 2003; Kravchick et al. 2005; Tombal et al. 2005). Contrary to this, impacted ureteral stones with little urine surrounding them have been reported to be difficult to fragment (Zhu et al. 2002). As mentioned above, from the physical standpoint, addition of fluid through a ureteral catheter could increase cavitation activity near the stone, resulting in faster stone comminution; however, clinical data is controversial. Seitz et al. (2006) reported that the presence of stone induced hydronephrosis does not affect the time to stone clearance or success rate after SWL in patients with proximal ureteral stones. According to a prospective randomized

study published by El-Assmy et al. (2007), the degree of hydronephrosis caused by the stone does not affect SWL outcome in cases with solitary lumbar ureter stones. An analysis of SWL by Demirbas et al. (2004) in patients with a solitary calculus in the distal ureter showed that the degree of urinary obstruction does not affect stone clearance. Other authors reported that for solitary lumbar ureter stones, the degree of hydronephrosis did not affect SWL outcome. Nevertheless, stones in obstructed systems were associated with longer stone clearance times, probably due to reduced peristalses (El-Assmy et al. 2007).

The presence of simple renal cysts (SRC), i.e., abnormal, fluid-filled sacs, close to a kidney stone may also affect SWL outcome. SRC are not a contraindication to SWL; however, little is known about their effect on stone comminution. Alenezi et al. (2016) published a comparative study of calculi fragmentation in an in vitro model mimicking SRC. According to their results, the presence of a cystic cavity was associated with the production of smaller fragments by SWL.

A common cause of unsuccessful treatment outcomes is shock wave absorption by intestinal gas, ribs, spine, sacroiliac skeleton and other pelvic bone structures (Tiselius and Chaussy 2012). If shock waves are coupled into the patient from the abdominal side, intestinal gas might reduce shock wave energy. In this case it is preferable to postpone the treatment. SWL protocols for patients having renal anomalies should be designed according to each case by an experienced staff. A general recommendation is not to perform SWL when the patient's blood pressure is above 160/100 mmHg. This is especially important for treatments during which the shock waves pass through renal tissue (Tiselius and Chaussy 2012).

Severe SWL-related complications are uncommon; however, hematomas or septicemia can lead to life-threatening situations (Chaussy et al. 2014). Complications after SWL include pain, hematuria, urinary tract infection, subcapsular or perirenal hematoma, loss of renal function and residual calculi (Roth and Beckmann 1988; Di Grazia 2010). The risk for asymptomatic and symptomatic hematoma is about 4 and 1 %, respectively (Türk et al. 2015). Steinstrasse is another well-known complication that may occur after SWL of large renal or ureteric stones (Al-Awadi et al. 1999; Tombolini et al. 2000; Sayed et al. 2001; Puppo 2006; Lucio II et al. 2011). Some authors have reported that stone fragment passage is facilitated by placing a stent before SWL; however, its usefulness has been controversial (Cass 1994; Harada et al 1994; Stoller and Bolton 2000; Butt et al. 2005). Shen and colleagues (2011) published the results of a systematic review on the outcomes of SWL in the management of upper urinary stones with or without Double-J stenting before treatment. Their results revealed advantages of stenting before SWL in terms of Steinstrasse. Nevertheless, stenting did not increase the stone-free rate and did not reduce auxiliary treatment after SWL, but it induced more lower urinary tract symptoms.

Asymptomatic residual fragments immediately after SWL are common; however, the percentage of stone-free patients increases after more than 3 months. Elimination of fragments from the lower pole calyx may take several months. According to an extensive analysis performed by Rassweiler et al. (2001), clinically insignificant residual fragments (CIRF) may still pass through the urinary tract up to 24 months after

SWL, indicating that the SFR after three months does not reveal the final treatment outcome. The term CIRF is debated because any fragment may form a nucleus for new stone growth.

Repeated SWL sessions at short intervals are not advisable; however, so far there is no consensus on the minimum recommended time between two consecutive extracorporeal therapies. The impact of shock waves on the kidney is comparable to a blunt trauma and causes parenchymal edema which subsides after 1 week; therefore it is advised to interspace subsequent SWL treatments at least 1 week. A minimum 2-week interval has been suggested by some authors (Chaussy et al. 2014). A study by Schnabel et al. (2015) revealed that in Germany the established minimum interval ranges between one day (in 7 % of the lithotripsy centers), and more than a week (in 26 % of the centers). About 39 % of the German lithotripsy centers consider that a two-day interval between SWL treatments is enough, 16 % wait between three and seven days and 10 % do not repeat SWL at all.

More information on SWL treatments and auxiliary procedures, complications and their prevention can be found in the literature (Fuchs et al. 1988; Evan and McAteer 1996a; Evan et al. 1998b; Sayed et al. 2001; Dhar et al. 2004; Puppo 2006; Skolarikos et al. 2006; Willis et al. 2006; da Cunha Lima et al. 2007; Evan and Willis 2007; Naja et al. 2008; Sarica and Yencilek 2008; Sighinolfi et al. 2008; Ather et al. 2009; Montag et al. 2010; Tiselius et al. 2010; Alsaikhan and Andonian 2011; Falahatkar et al. 2011; Hiros et al. 2011; Vicentini et al. 2011; Sugihara et al. 2012; Tiselius and Chaussy 2012).

SWL has been associated with hypertension and diabetes mellitus type 2 (DM2) (Janetschek et al. 1997; Krambeck et al. 2006). At 19 years of follow-up Krambeck and colleagues (2006) found that the incidence of hypertension and DM2 was significantly higher than in a cohort of conservatively treated patients with renal and proximal ureteral stones; however, a few years later the same group (Krambeck et al. 2011) reported that SWL is not predictive of hypertension at long-term follow-up. The authors comment that referral bias and lack of long-term follow-up have been limitations of previous studies. Other reports revealed that there should be no concern on shock wave-induced DM2. For instance, Sato et al. (2008) published that SWL for renal and ureteropelvic junction (UPJ) stones is not associated with hypertension and DM2. According to results published by Eassa et al. (2008), SWL has no significant long-term effects on renal function or blood pressure regardless of the type of lithotripter used and regardless of the BMI. Makhlouf et al. (2009) collected data on the presence and onset of DM2 in almost 2000 patients treated with SWL to analyze the hypothesis that shock waves increase the incident risk of new-onset DM2. The mean age of the patients was approximately 52 years at SWL and the median follow-up was 6 years. Their statistical analysis revealed that SWL-treated patients did not develop DM2 at a greater rate than does the general population. Furthermore a retrospective review of 727 patients who underwent SWL revealed no association between shock wave treatment and the development of hypertension or diabetes in a multivariate analysis (Chew et al. 2012), and in a large population-based cohort of shock wave-treated patients, Krambeck et al. (2011) also could not associate SWL with hypertension.

Handa et al. (2014) exposed the left kidney upper pole calyx of miniature pigs up to 4000 shock waves (voltage 24 kV; shock wave rate 2 Hz) using an unmodified Dornier *HM3* lithotripter to determine whether SWL to pigs with metabolic syndrome would worsen glucose tolerance or increase the risk of DM. Six months prior to the shock wave session, the pigs were fed a special diet to induce metabolic syndrome. The authors reported biochemical and histological evidence that shock wave treatment of the left kidney upper pole can injure the pancreatic tail; however, the injury did not alter the glucose tolerance and insulin sensitivity. Therefore, they concluded that SWL to the kidney does not intensify metabolic syndrome (MetS) features. The same research group performed another study with four miniature pigs to assess whether renal SWL (2000 shock waves; voltage 24 kV; shock wave rate 2 Hz) influences MetS onset and severity (Handa et al. 2015b). Shock waves, generated with the aforementioned lithotripter, were focused on the upper pole of the left kidney of two animals. Arterial blood pressure was measured via an implanted radiotelemetry device. MetS development was determined by the intravenous glucose tolerance test. According to these preliminary results, MetS progression and severity were similar in the two groups (shock-wave treated and sham-treated pigs). Arterial blood pressure increased about two months after shock wave therapy. The authors concluded that shock wave exposure of the kidney seems not to be a risk factor for worsening glucose tolerance or DM onset. Nonetheless, it could be a risk factor for early onset hypertension. In another study, Handa et al. (2015a) fed nine-month-old pigs with an excess calorie atherogenic diet to induce MetS. At 15 months of age, the upper pole calyx of the left kidney of each pig was treated with 2000 or 4000 shock waves (*HM3* voltage 24 kV; shock wave rate 2 Hz). Serum creatinine and blood urea nitrogen values were within normal limits before shock wave treatment and remained unchanged after treatment in both the low and the high dose-treated pigs. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) of kidneys treated with SWL at either dose was similar to the contralateral non-treated kidneys. These results support the opinion that a single shock wave treatment session does not result in renal impairment, even in patients with MetS.

SWL may damage the medullary collecting ducts and vasa recta, which are sites for urine pH regulation. Evan et al. (2015) tested the hypothesis that SWL raises urine pH and therefore calcium phosphate supersaturation. To do so, the left kidney of nine pigs was exposed to shock waves. Metabolic studies were performed using bilateral ureteral catheters for up to 70 days after shock wave-treatment. Histopathological studies followed at the end of the study. The mean pH of the left kidneys exceeded that of the control kidneys by 0.18 units in 9 pigs. Tubule cell injury was observed in shock wave-treated kidneys. Nephron loss and fibrosis were found in the cortex and the medulla. This leaded to functional disturbances across a wide range of electrolyte metabolism including higher than control urine pH. Under normal conditions, the non-treated kidney would compensate for the aforementioned variations so that the reported disorder would be of no interest except for the potential of higher pH to engender calcium phosphate stones.

Because SWL depends on many factors, success is often difficult to predict. Nevertheless, experience has led to general recommendations, mathematical models

and nomograms that may help the urologist to predict renal and ureteral stone SWL outcomes (Kanao et al. 2006; Vakalopoulos 2009; Wiesenthal et al. 2010, 2011; Tran et al. 2015). According to an analysis by Vakalopoulos (2009), the sex, SSD, the age and the BMI of the patient; the size, the volume and density of the stone, as well as the presence of multiple stones affect the statistical significance for stone-free rates. The author published an equation to assist in predicting SWL outcomes. The equation also depends on the lithotripter used and could be an aid to achieve maximum efficacy and safety at minimum cost.

Tissue exposure can be reduced if the focal zone is targeted exactly on the specific region to treat, so that the energy reaches therapeutic values only in the needed volume. As mentioned before, shock wave-focusing sources produce cigar-shaped focal zones. Because the object or region to be treated has a different shape, there will always be unneeded shock wave-treated tissue (Fig. 3.7). Since this cannot be avoided it is crucial to stop shock wave treatment on time. The number of shock waves per treatment and the voltage setting on a lithotripter are risk factors that limit the extent to which SWL should be used (Janetschek et al. 1997; Willis et al. 2005).

In some lithotripsy centers, the operation of the extracorporeal lithotripter is left to new residents or technicians with little training, significantly reducing the success rates. To improve treatment outcomes, urologists should have basic knowledge of shock wave physics and understand how the components of their extracorporeal lithotripter operate (Rassweiler et al. 2005, 2011; Bailey et al. 2006; Cleveland and McAteer 2007; Loske 2007; Wadhwa 2011; Chaussy and Tiselius 2012; Tiselius and Chaussy 2012; Chaussy et al. 2014). To reduce tissue injury and guarantee optimal fragmentation efficiency, shock waves should always be administered with care by well-trained personnel, under supervision of an urologist certified in SWL (Eichel et al. 2001; Jagtap et al. 2014). The importance of having a specialized SWL-team often has been underestimated (Knoll et al. 2011; Tiselius and Chaussy 2012; Neisius et al. 2015). Institutional preset protocols for large groups of patients are a common cause of over-treatment. Well-defined protocols, designed according to each patient are crucial to guarantee good results and prevent treatments with low probability of success. Excellent extracorporeal lithotripters may produce poor clinical outcomes if not used properly. Normally more attention is given to the type of lithotripter than to the team that is using it. Similar outcomes may be obtained with different lithotripters if the treatment protocols are well designed (Bhojani et al. 2015). Nowadays, most stones can be managed using ureteroscopic techniques. Nevertheless, whenever there is a high probability of successful treatment outcome with one SWL, shock waves should be chosen.

5.7 Shock Wave Lithotripsy for Gallbladder, Pancreatic and Common Bile Duct Stones

Gallstones are formed in the gallbladder when substances in the bile create hard particles. Eighty percent of gallstones are composed of cholesterol. Cholesterol gallstones predominate in western countries and approximately twice as many

women experience cholelithiasis than men (Acalovschi 2001). Bile pigments or calcium may also form calculi. In Europe and the USA the prevalence of gallstones in adults is approximately 10 to 15 % (Portincasa et al. 2006; Shaffer 2006). Gallstone disease is a major cause of hospitalization, although many gallstones do not cause symptoms. Risk factors are obesity and DM2, among others. The presence of a gallstone in the common bile duct is referred to as *choledocholithiasis*. Bile duct stones are gallbladder calculi that have moved out of the gallbladder and became lodged in the common bile duct which merges with the pancreatic duct (PD). About 14 % of the patients with gallstones develop stones in the common bile duct. Analogously, pancreatic stones develop from calcium deposits in the pancreas and may obstruct the flow of enzymes from the pancreas to the small intestine. Up to 30 % of patients with chronic pancreatitis are stone formers.

As mentioned in Chap. 2, the disintegration of urinary and biliary calculi using continuous wave ultrasound was proposed long ago; however, the technique was abandoned, because the in vivo experiments resulted in significant tissue damage (Lamport et al. 1950; Mulvaney 1953; Coats 1956). After the success of shock waves to pulverize urinary calculi, attempting to treat other stones in the human body was a logical consequence. Initial in vivo experiments on SWL of gallstones were published approximately three years after the first SWL in urology and several studies followed (Brendel and Enders 1983; Delius et al. 1988a; Becker et al. 1989; Deaconson et al. 1989; Ell et al. 1989; Neisius et al. 1989a; Ponchon et al. 1989a; Vergunst et al. 1990).

The short- and long-term effects of biliary SWL in pigs were investigated by Vergunst et al. (1993b). Analogous to the initial in vivo experiments performed by Chaussy et al. (1979a) in dogs, single human gallstones were implanted into the gallbladders of pigs and exposed to 4000 or 8000 shock waves using an electromagnetic lithotripter. A group of animals was sacrificed one day after SWL; another group was sacrificed 1 week after treatment, and a third group was sacrificed after one year. Tissue damage was mostly reversed within 1 week, and after one year only small hepatic scars were seen. Stone fragments smaller than 5 mm were obtained in 41 % of the SWL-treated pigs. No statistically significant differences in tissue damage and stone fragmentation were observed after 4000 versus 8000 shock waves.

The first shock wave treatments for gallbladder stones performed in 1985, as well as many other studies revealed that shock waves are safe and efficient to disintegrate solitary gallbladder stones in selected patients (Sauerbruch et al. 1986; Vergunst et al. 1989; Barkun and Ponchon 1990; Mulagha and Fromm 2000; Rabenstein et al. 2005). Electrohydraulic (Sackmann et al. 1988; Ponchon et al. 1989b; Schoenfield et al. 1990), electromagnetic (Classen et al. 1990) and piezoelectric (Hood et al. 1988; Ell et al. 1990) lithotripters have been used. Initial SWL of gallbladder stones using piezoelectric lithotripters was reported to be painless (Hood et al. 1988), tissue damage seemed to be temporary and side effects were rare (Stephenson et al. 1989). Sackmann and his group published the outcomes of 175 SWL treatments for gallbladder stones. 72 % of the patients having solitary stones with a diameter of up to 30 mm in diameter and 63 % of the patients with multiple calculi were free of stones 1 year after shock wave and oral dissolution therapy (Sackmann et al. 1988). In the early 1990s, SWL was one of the most promising

noninvasive treatment modalities for cholelithiasis; however, this perception changed with time. Even if SWL was effective in treating selected patients, the high gallbladder stone recurrence was an issue (Portincasa et al. 1996; Sackmann et al. 1993; Venneman et al. 2001).

Complete spontaneous drain of gallbladder stone debris after SWL is rare, because most fragments may not drain into the intestine on their own (Greiner et al. 1990). The choledochoduodenal sphincter and the spiral valves in the cystic duct may obstruct the passage of stone debris and if sufficient disintegration is not obtained, endoscopic extraction is necessary (Bland et al. 1989; Chapman et al. 1989; Wenzel et al. 1989; Sackmann 1992; Nahrwold 1993; Chang and Pamies 1994). Furthermore, the fluid surrounding a gallstone has a higher viscosity than urine, suppressing cavitation and reducing the production of cavitation-induced microjets and the fragmentation efficiency of shock waves. When treating gallbladder stones with shock waves it is common that residual fragments are left and need to be dissolved by chemical solvents such as ursodiol (Burnett et al. 1989; Ponchon et al. 1989b). Methyl tert-butyl ether (MTBE), an organic cholesterol solvent, has also been proposed (Vergunst et al. 1994); however, it did not become popular because of its potential toxicity.

Even if patients with multiple gallstones, some of them larger than 30 mm, have been treated effectively, the success rate is low. Because stone fragment passage is much more difficult than with urinary calculi, in general patients having large or multiple gallstones are not eligible for shock wave treatment (Pauletzki et al. 1997). Patients having coagulation disorders should not be treated with shock waves. Care should be taken with gas-filled intestines, because shock waves may cause tissue damage in the upper gastrointestinal tract (Karawi et al. 1987).

Most gallstones are radiolucent and only can be detected fluoroscopically by contrast opacification of the gallbladder using intravenous or oral cholecystography. Radiolucent gallbladder stones may be targeted by ultrasound; however, this can be difficult in obese patients. Common bile duct stones are more easily localized by fluoroscopy than using sonography. Soft cholesterol stones (low density on CT) are more ductile and more shock waves are required for fragmentation than for calculi with high calcium content. The usefulness of CT to predict the chemical composition of gallstone has been questioned by some authors (Baron 1991; Brink and Ferrucci 1991). Brakel et al. (1990) and Vergunst et al. (1993a) managed to reliably identify pure cholesterol stones using a cut-off point of 140 and 110 HU for the mean CT attenuation numbers, respectively. However, care should be taken when comparing cut-off points because, as mentioned before, they depend on the CT system used. To make reliable comparisons, reference calibration phantoms have to be used and CT numbers have to be converted to equivalent values of milligrams of K_2HPO_4 per ml. Several authors have reported an inverse relation between cholesterol content and CT attenuation and some of them also found a reliable correlation between calcium content and CT attenuation numbers (Hickman et al. 1986; Baron et al. 1988; Barkun and Ponchon 1990; Brakel et al. 1990).

Nowadays, gallbladder SWL is only used in very few centers and laparoscopic cholecystectomy has become the standard treatment for gallbladder stones

(Portincasa et al. 2012). Nevertheless, shock waves can be used to treat patients with bile duct stones that resist removal after endoscopic sphincterotomy or in patients where surgery is contraindicated (Becker et al. 1987; Brown et al. 1988; Burhenne et al. 1988; Sauerbruch and Stern 1989; Sackmann et al. 2001).

Sauerbruch and colleagues reported the results of SWL to patients having pancreatic stones using a Dornier *HM3* and concluded that a combined approach by endoscopy and SWL appears promising (Sauerbruch et al. 1987, 1989). Even if endoscopic manipulations may sometimes be needed, SWL has been considered as the first-line therapy for selected patients with large pancreatic and common bile duct (CBD) stones (Delhaye et al. 1992; Inui et al. 2005; Tadenuma et al. 2005; Tandan and Reddy 2011; Suzuki et al. 2013). SWL of retained CBD stones should be considered before surgery, especially in elderly or high-risk patients (den Toom et al. 1991). Several authors reported that extracorporeal shock waves achieved duct clearance in up to 50 % and improvement in duct decompression in up to 70 % of patients with PD calculi (van der Hul et al. 1993, 1994; Choi et al. 2005; Kim 2005; Tadenuma et al. 2005; Choi and Kim 2006; Conigliaro et al. 2006). There is a consensus that comminution of PD stones with shock waves, assisted by endoscopic clearance of the main PD significantly improves the outcomes in patients with chronic pancreatitis (Kozarek et al. 2002). Rubenstein et al. (2002) performed pancreatic SWL in 23 patients with two different lithotripters. After shock wave treatment, endoscopic retrograde cholangio-pancreatography (ERCP) was performed. Their main conclusion was that combined with ERCP pancreatic SWL is an effective and safe procedure, particularly for stones smaller than 20 mm. Guda et al. (2005) published an evaluation of SWL with or without endoscopic therapy in PD clearance. According to their results, SWL in combination with endoscopic therapy seems to be effective in relieving PD obstruction and reducing pain in chronic calcific pancreatitis.

In combination with endoscopy, SWL also has shown to contribute to pancreatic ductal decompression in patients with chronic calcific pancreatitis (CCP) (Brand et al. 2000; Dumonceau et al. 2007; Tandan et al. 2010). Partial pain relief in 85 %, complete pain relief in 50 %, and avoidance of surgery in 84 % of patients with CCP was reported by Seven et al. (2012). Tandan et al. (2013) evaluated the intermediate and long-term results of shock wave treatment to patients suffering from calcific pancreatitis with unknown pathogenesis and concluded that SWL offers good clinical outcomes for large PD calculi. ERCP ductal drainage after SWL has proven to be safe to clear multiple main PD stones in patients with tropical pancreatitis (pancreatitis mostly seen in young people of tropical countries, involving the main PD and resulting in large ductal calculi) (Ong et al. 2006). According to results published by Parsi and colleagues (2010), SWL of obstructive PD stones in patients with recurrent attacks of acute pancreatitis can prevent further attacks.

Even if SWL combined with endoscopic drainage of the main PD is an attractive alternative to surgery, it is not used frequently, because extracorporeal lithotripters are expensive and not always available. A solution to this may be the use of small handheld lithotripters designed for SWL of salivary gland stones and ESWT. Milovic et al. (2011) modified a *Minilith SL1* (Storz Medical AG) to treat 32 patients with chronic

calcific pancreatitis in whom previous endoscopic stone removal had failed. After shock wave treatment, complete stone clearance or stent insertion was possible in all patients. Because small shock wave sources designed for ESWT are less expensive, the future trend may be their modification to be used in some SWL applications.

5.8 Shock Wave Lithotripsy for Salivary Gland Stones

Sialolithiasis, i.e., salivary gland lithiasis, is a common pathology of the salivary glands, causing swelling and pain, which accounts for approximately 30 % of all salivary disorders. It has been reported that males are affected much more than females (Cawson and Odell 1998). Salivary stones may form in any of the salivary glands, such as the large paired glands, the submandibular glands, the parotid glands and the sublingual gland. In 2009 it was reported that its incidence was estimated to be about 0.15 % (Harrison 2009). Up to 92 % of calculi are found in the submandibular gland and 6 % in the parotid gland. Most calculi consist of hydroxyapatite and carbonate apatite, together with an organic matrix and may contain small amounts of magnesium, potassium and ammonia. Surgical removal of the affected gland is necessary if the stone cannot be eliminated by dilatation or dissection of the salivary duct. This may involve a risk to adjacent structures such as the facial nerve. The introduction of SWL to treat patients suffering from salivary gland calculi in the 1990s significantly changed the therapeutic approach of sialolithiasis (Schmitz et al. 2008).

The first in vitro fragmentation of a sialolith using shock waves was reported by Marmary (1986). Destruction of the calculus placed at the *F2* focus inside the water-filled tub of an *HM3* lithotripter in a small water-filled plastic bag was achieved after 50 shock waves. This study was followed by an experiment to analyze the feasibility of using an electromagnetic lithotripter (*Lithostar*, Siemens Healthcare GmbH) to pulverize salivary gland stones (Brouns et al. 1989). Even if in vitro fragmentation was achieved, shock wave treatment was not carried out on patients because of the potential damage to the dentition. The development of piezoelectric lithotripters by Richard Wolf GmbH, facilitated the first treatments of patients suffering from sialolithiasis (Iro et al. 1989, 1990b). Previous in vitro and in vivo experiments showed that SWL of salivary stones is feasible, if an accurate patient positioning and exact stone location is guaranteed (Iro et al. 1990a, 1991).

Iro and colleagues (1992) published the results of SWL on 51 patients with symptomatic solitary salivary stones that could not be removed by conventional procedures. In approximately 70 % of patients the stones were located in the submandibular gland and in the rest of the patients the stones were in the parotid gland. Shock waves were generated with a piezoelectric lithotripter and focused on the stones under real-time ultrasonic monitoring, without using anesthesia, sedatives, or analgesics. Fragments smaller than 3 mm were obtained in 88 % of the patients. Localized petechial hemorrhages were observed in 13 % and transient swelling of the gland in 3 % of the treatments. Twenty weeks after SWL 90 % of the patients were free of pain and 53 % were stone free. No long-term tissue damage was observed during follow-up.

Hessling et al. (1993) published the results of a prospective study of electromagnetic SWL to 25 patients having 33 salivary stones (mean diameter approximately 7 mm). Stone targeting was performed using ultrasound after application of local anesthesia. An adequate disintegration was achieved in 82 % of the parotid gland stones and in 14 % of the submandibular gland stones. All patients were clinically free of symptoms after the treatment; however, only four patients were completely stone free. The authors concluded that considering the risk of parotid surgery, SWL is indicated for stones distally located from the masseter banding of the parotid duct; however, for stones in the outlet path system of the submandibular gland, the indication of a shock wave treatment should be viewed critically, because of its low success rate and the low risk of surgery. Kater and colleagues (1994) reported that approximately 60 % of the SWL-treated patients with parotid gland stones or submandibular gland stones obtained either total stone clearance or sufficient fragmentation to permit spontaneous passage.

Lithotripters with a large focal zone, such as electrohydraulic devices, are not suitable to treat salivary calculi (Bayar et al. 2002); however, both electromagnetic and piezoelectric lithotripters have been used with good results. Motivated by the success achieved in treating salivary gland stones with extracorporeal lithotripters that were originally produced to comminute urinary stones, some manufacturers designed smaller and more versatile shock wave sources to treat patients suffering from sialolithiasis. Fokas and colleagues (2002) performed an average of 2.1 SWL sessions on patients with sialolithiasis of the parotid gland and an average of 3.1 sessions on patients with sialolithiasis of the submandibular gland using an electromagnetic *Minilith SL1* lithotripter equipped with an in-line ultrasound transducer, manufactured by Storz Medical AG. This was the first lithotripter (also called *sialolithotripter*) designed for this purpose. The treatments were done on an outpatient basis and in most sessions without anesthesia or analgesia. Up to 3000 shock waves were applied per session. Minor pain, swelling, bleeding out of the intraoral orifice and skin petechiae were the only complications. All patients were symptom-free after SWL; however, stone fragments remained in the parotid gland in about 18 % and in the submandibular gland in approximately 33 % of the patients.

A 10-year follow-up study to evaluate the efficiency of SWL in 19 patients suffering from salivary stones was reported by Andretta et al. (2005). The role of radiography, ultrasonography and MRI in the diagnosis of sialolithiasis was also analyzed. Treatment consisted of four shock wave sessions (1200 shock waves each) performed using a *Minilith SL1* (Storz Medical AG) with a coaxial ultrasound transducer (7.5 MHz). Treatment outcomes revealed a greater efficiency of shock wave therapy for stones localized in the parotid gland. In almost 70 % of the cases, SWL was resolutive after ten years and patients were free of symptoms. MRI produced sialographic images without the need of contrast medium and without the disadvantage of ionizing radiation. Obvious inconveniencies are high costs, long scanning times, and the presence of artifacts in patients with dental bridges or prosthesis.

The results of a retrospective multi-center analysis of almost 4700 patients treated in Germany, United Kingdom, Israel, Italy and France for salivary gland stones with minimally invasive techniques, was published in 2009 (Iro et al. 2009). More than 50 % of a total of 2102 patients treated with SWL became free of calculi,

and in an additional 26 % the symptoms improved. Desmots et al. (2014) reported the results of a prospective follow-up of 25 patients over a period of 31 months with one or more salivary calculi treated with SWL. Each patient received three lithotripsy sessions of 5000 shock waves without anesthesia or analgesia, using a *Minilith SL1* (Storz Medical AG). The authors defined complete success as resolution of symptoms and disappearance of stones on ultrasound. SWL was more efficient for parotid than for submandibular calculi. Absence of clinical symptoms 3 months after the end of the treatment or after the last session, and residual stones smaller than 2 mm were observed in 36 % of the cases. Partial success was achieved in 48 % of the patients. The total energy delivered, and the number of shock waves, were predictive factors of complete success.

Nowadays, it is generally accepted that the effectiveness of shock waves to eradicate sialolithiasis mainly depends on the size of the stones (Escudier et al. 2010). SWL is generally used to disintegrate stones that are either too difficult to access with an endoscope or too big for endoscopic lithotripsy (Zenk et al. 2014). The radiodensity of the stones plays a less important role. SWL is more efficient in treating parotid calculi than submandibular stones. The treatment is relatively painless, generally does not require anesthesia and can be done on an outpatient basis. It is an attractive alternative for stones smaller than 7 mm (Ottaviani et al. 1996; Fokas et al. 2002; Escudier et al. 2003; Capaccio et al. 2004; Zenk et al. 2004; McGurk et al. 2005). The maximum recommended number of shock waves per session with piezoelectric and electromagnetic shock wave sources is 3000 and 7500 shock waves, respectively (Zenk et al. 2014). Energy flux densities between approximately 0.4 and 0.8 mJ/mm^2 have been used. Contraindications are the presence of a heart pacemaker, acute inflammation of the salivary gland, oral anticoagulation, pregnancy, and failure of stone detection by ultrasound (Aidan et al. 1996). Ear protectors are recommended for the patient. Side effects are not to be expected after SWL if the treatment is performed with a small-focal-volume shock wave source (piezoelectric or electromagnetic) and precise positioning of the patient using sonographic location (Zenk et al. 2014).

5.9 Development and Future of SWL

Well-designed case-oriented treatment protocols as well as a thorough patient selection will get more popular among lithotripsy centers around the world and increase the success rates of SWL (Neisius et al. 2015). Returning SWL into the hands of well-trained, experienced urologists is crucial to manage the increase in stone patients.

Although SWL is a routine in most countries and millions of treatments have been performed successfully, improvements to increase fragmentation efficiency and reduce tissue damage and pain are still being sought (Lingeman et al. 2009; Zhong et al. 1999b; Rassweiler et al. 2013, 2014). Improvement of SWL should concentrate on both lithotripter design and treatment protocols. Misconceptions regarding urinary stone comminution mechanisms, as well as treatment parameters like dose, intensity,

energy and focal area are still common. Nowadays, most extracorporeal lithotripters have elegant multifunctional designs, improved imaging systems and are relatively easy to operate; however, clinical results achieved with newer systems are often not better than those obtained with the previous models (Rassweiler and Alken 1990; Wilson and Preminger 1990; Lingeman 1996, 2007; Skolarikos et al. 2006; Köhrmann 2007; Preminger et al. 2012; Rassweiler et al. 2010, 2014). Furthermore, there is still no consensus on some important topics. It is remarkable that, more than 35 years after the first SWL, the *HM3* lithotripter is sometimes still referred to as the gold standard because of its stone-free rate and minimal re-treatment rate. The ample experience of the urologists performing the treatments in the early days of SWL certainly contributed to the excellent clinical outcomes.

Since the shock wave source represents the most important element of a lithotripter, much research has been focused on designing shock wave generators to emit pressure profiles that reduce tissue damage while enhancing stone comminution. Some companies switched from one shock wave generation mechanism to another or modified their design to cover a wider spectrum of clinical cases. Dornier MedTech GmbH, the pioneer of SWL that developed famous electrohydraulic lithotripters, such as the *HM3*, *HM4* and *MFL 5000*, switched to electromagnetic shock wave generation during the 1990s (Sheir et al. 2003b). The Chinese company Suzhou XiXin Medical Instruments Co. Ltd., is selling the large-focus electromagnetic lithotripter described in Sect. 5.3.4 (model *CS-2012A-3*), and also an electrohydraulic lithotripter with a much smaller focal zone (model *CS-2000A*). Direx Systems Corporation switched from electrohydraulic lithotripters to the electromagnetic system mentioned in Sect. 5.3.3. As already explained, other companies manufacture lithotripters with variable focal zones, such as the *Piezolith 3000 plus* (Richard Wolf GmbH) and the *Modulith SLX-F2* (Stroz Medical AG).

A phenomenon that may be considered in the design of shock wave sources is the shift in the locations of the peak-positive (p^+) and peak-negative pressure (p^-). Focusing of positive and negative pressure waves is not equal. This is a consequence of the nonlinear nature of the shock wave field. In the 1990s, Coleman and colleagues (1993) found maximal cavitation in a region several millimeters in front of the second focus (closer to *F1*) of an electrohydraulic shock wave source. Because intense cavitation is produced at the spot where the negative pressure has its largest amplitude, it seems reasonable to place the calculi and not the tissue at this spot. In electrohydraulic lithotripters p^+ tends to shift away from the reflector more than 10 mm from *F2* when using high-voltage settings, whereas p^- shifts towards the reflector by up to 20 mm (Qin et al 2010; Sokolov et al. 2002; Zhu et al. 2002; Zhou and Zhong 2006). Sokolov et al. (2002) suggested placing the stone not at *F2*, but 20 mm closer to *F1*. Using an *HM3* lithotripter, they observed increased comminution by aligning the stone on the beam axis, closer to *F1*. With dual passive cavitation detection (DPCD) it was possible to record increased bubble collapse radiated pressure at the spot of the maximum peak-negative pressure. In a similar study, Fonseca (2005) reported that a Direx *Tripter Compact* was equally efficient in breaking stones at any point between *F2* and 20 mm proximal to *F1*. Unfortunately, the opposite shifts in peak-positive and peak-negative pressures generated by electrohydraulic shock wave generators do not allow placing the stone both at the focal spot (p^+) and at the location of maximum cavitation.

By exposing well standardized kidney stone phantoms to shock waves inside an experimental electrohydraulic shock wave source, it could be demonstrated that the fragmentation efficiency of all stone phantoms improved when positioning them 10 mm below the geometrical focus *F2*, i.e., closer to *F1* (Loske 2010). In another part of the study, rectangular (30×30×14.3 mm) HMT kidney stone models (High Medical Technologies, Kreuzlingen, Switzerland) were exposed to shock waves using the same lithotripter to compare the shape and size of the craters produced at different energy settings and positions of the stones. Using a discharge voltage of 20 kV, the largest craters were observed at $F2-10$ mm and at $F2-20$ mm for degassed and non-degassed water, respectively. Shock waves in non-degassed water produced largest craters, confirming that cavitation is the main erosion mechanism.

Duryea et al. (2013) investigated how cavitation-based histotripsy stone erosion can be synchronized with lithotripter shock waves to enhance stone comminution. Histotripsy ultrasound pulses at a pulse repetition frequency of 100 Hz were used in combination with lithotripter shock waves ($p^+=34$ MPa, $p^-=-8$ MPa) at a shock rate of 1 Hz to pulverize kidney stone phantoms in vitro. Stones were sonicated with five different treatment protocols (a) shock waves with bursts of histotripsy interleaved between successive shock waves, (b) shock waves followed by bursts of histotripsy, (c) bursts of histotripsy followed by shock waves, (d) only shock waves, and (e) only histotripsy bursts. Histotripsy following shock waves resulted in the greatest degree of stone fragmentation. Shielding induced by remnant histotripsy bubble nuclei apparently reduced the fragmentation efficiency when bursts of histotripsy were emitted between one shock wave and the next. The authors concluded that their future work will be to design pulse sequences for actively mitigating the shielding effect.

A method to eliminate bubbles from the shock wave path using low-amplitude acoustic pulses was proposed by Duryea et al. (2014). Microbubbles generated by preceding shock waves persist along the shock wave path and may attenuate the negative phase of following shock waves. The acoustic pulses, designed to stimulate the aggregation and coalescence of undesired bubbles, were generated by a piezoelectric transducer and fired orthogonal to the shock wave propagation axis, towards the focal zone of a research electrohydraulic shock wave lithotripter. In vitro stone fragmentation tests were performed at different shock wave rates with or without the bubble-removal pulses. The results revealed that removing bubbles improved the fragmentation efficiency at shock wave rates of 1 and 2 Hz. At a shock wave rate of 0.5 Hz stone fragmentation efficiency was not enhanced by using the bubble-removal system, because the remnant microbubbles had sufficient time to dissolve. A different solution to remove bubbles along the shock wave path was proposed by Lautz et al. (2013). A jet of degassed water was implemented inside the coupling cushion of a lithotripter to remove cavitation nuclei and improve in vitro stone fragmentation efficiency. Further development of bubble-removal systems could result in more efficient SWL.

Nowadays, an extracorporeal lithotripter should be a multifunctional endourological workstation, with both high quality state-of-the-art ultrasound and fluoroscopic imaging systems, and a radiotranslucent treatment table that is accessible

from all sides, with a capacity to treat both children and obese patients. It is expected that improved extracorporeal shock wave lithotripters will still be used to treat small stones for many years (Rassweiler et al. 2013). Promising innovations to enhance stone pulverization and patient comfort, while reducing tissue trauma with the lowest re-treatment rates, are the development of automated stone tracking throughout the whole treatment (hit-control), feedback systems to determine the status of stone fracture and the instant when stone comminution should be considered as completed, movable shock wave heads with unlimited coupling positions, efficient real-time shock wave coupling supervision, and reliable noninvasive stone analysis. Advances in imaging technology and computer simulation, as well as in computer-assisted patient positioning and shock wave navigation will certainly contribute to improve extracorporeal lithotripters. Twin-pulse techniques, applying shock waves coming from variable angles, modified tandem shock wave profiles (Sect. 4.7) (Canseco et al. 2011), novel lenses for electromagnetic lithotripters (Sect. 5.3.1) (Neisius et al. 2014), and highly versatile multichannel discharge shock wave generators (Sect. 5.5.4) (Lukes et al. 2012a) may also increase the efficiency of SWL. Furthermore, auxiliary measures such as extracorporeal ultrasound-induced repositioning of renal stones from unfavorable sites like the lower calyx to the renal pelvis and assistance to a better clearance of stone fragments will contribute to improve treatment outcomes (Shah et al. 2010b, 2012). Harper et al. (2013) studied the feasibility of in vivo ultrasonic propulsion in pig kidneys. Stones were ureteroscopically implanted in the renal pelvicalyceal system. Transcutaneous ultrasonic propulsion was used to relocate stones from the calyx to the renal pelvis, ureteropelvic junction or proximal ureter. The authors reported that the novel technique is safe and promising as an adjunct to manage renal calculi. The thresholds for tissue injury produced by focused ultrasound for renal calculi expulsion and a comparison with tissue injury from SWL were reported a year later by Connors et al. (2014).

Extracorporeal lithotripsy that uses short sinusoidal bursts of ultrasound, referred to as burst wave lithotripsy (BWL) is currently under investigation. Initial in vitro experiments revealed that BWL could be an alternative to SWL in the future (Thoma 2014; Maxwell et al. 2015). Bursts are generated at a much higher rate (200 Hz) than shock waves. Based on in vitro data, an advantage of BWL could be the ability to produce smaller fragments more quickly in even the toughest stones. Tissue heating is minimized because of the low temporal average intensity (approximately 15 W/cm^2). More research will be needed to fully explore the possibilities of BWL. So far all pre-clinical studies were encouraging (Sorensen et al. 2013; Harper et al. 2014), and the first successful treatment was reported by Harper et al. (2016).

Chapter 6
Extracorporeal Shock Wave Therapy

6.1 Introduction

The noninvasive treatment of musculoskeletal injuries and pain using shock waves generated outside the patient's body and delivered to the affected region to trigger the body's mechanisms to initiate natural healing called *extracorporeal shock wave therapy* (ESWT) has been attracting attention for many years (Heller and Niethard 1997; Siebert and Buch 1997; Thiel 2001; Haake et al. 2002a; Gerdesmeyer et al. 2007; Gerdesmeyer and Weil 2007; Dreisilker 2010a; El-Husseiny et al. 2010a, b; Helfmeyer 2010; Piontkowski et al. 2010; Gleitz 2011; Wang 2012; Lohrer and Gerdesmeyer 2014; Kertzman et al. 2015; Raveendran 2015; Schmitz et al. 2015). ESWT is sometimes also called *orthotripsy* (Ogden et al. 2001a), *extracorporeal shock wave application* (ESWA), or *shock wave biosurgery*, even if the word *surgery* is not appropriate to describe a noninvasive therapy. In some articles, the terms *acoustic wave therapy* (AWT) or *extracorporeal pulse activation therapy* (EPAT) are used, generally referring to *radial extracorporeal shock wave therapy* (rESWT). In many publications, including this chapter, the term ESWT is used even if the related therapeutic device generates radial pressure waves, not shock waves. The main differences between radial pressure waves and shock waves are explained in Chap. 3. Some ESWT equipment have two therapy heads, one generates focused shock waves and the other radial pressure waves. Focused, defocused, and planar pressure waves (Sect. 6.2) as well as radial pressure waves (Sect. 6.3) are utilized for ESWT and the list of indications is continuously growing (Mittermayr et al. 2012; Speed 2014; Lohrer and Gerdesmeyer 2014).

ESWT in the musculoskeletal system gained worldwide recognition because of good clinical results, especially with the treatment of calcifying tendonitis of the shoulder, proximal plantar fasciitis of the heel, lateral epicondylitis of the elbow, and non-union of long-bone fracture. It is considered when the patient has a diagnosis that is known to be responsive to shock waves or radial pressure waves, and when easier treatment modalities have failed. An ESWT typically lasts less than

30 min, producing mild side effects, such as tingling, aching, redness, or bruising in few cases. ESWT protocols vary from one to four sessions with an interval of several days between sessions. To treat a certain region inside the body, shock waves may be focused or not. Depending on the specific case, shock wave targeting can be aided by ultrasound (Beck 2013), fluoroscopy, or by the feedback of the patient. When there are no known contraindications to the procedure, shock waves or radial pressure waves are targeted directly to the pain causing area. ESWT may be a complementary therapy to surgery and other conventional treatment modalities in several orthopedic disorders. Unfortunately, the cellular and molecular working mechanisms for most, if not all, ESWT modalities are not fully understood.

Shock waves were introduced into areas different from lithotripsy because of an incidental observation of osteoblastic response during animal studies in the 1980s. They were also proposed as a technique to facilitate the removal of the femoral component and cement in revision of total hip arthroplasty (Karpmann et al. 1987). Braun and coworkers (1992) reported the effects of shock waves on the interface between human femoral segments and polymethylmethacrylate (PMMA) in vitro.

Today, many companies offer modified extracorporeal shock wave lithotripters or specially designed shock wave and radial pressure wave sources, suspended on articulated arms with three-dimensional movement. These systems use ballistic, electrohydraulic, electromagnetic, or piezoelectric transducers. Several devices have been approved by the US Food and Drug Administration (FDA) and considered as options for conditions not helped by traditional anti-inflammatory therapies, such as massage, physiotherapy, acupuncture, steroid injections, medications, or immobilization devices. As will be explained in Chap. 7, shock wave sources for the minimally invasive approach to vascular thrombolysis, selective dissection of tissues, and drug delivery have also been designed (Rosenschein et al. 1992; Belcaro et al. 1999; Kodama et al. 1999; Jagadeesh and Takayama 2002; Hosseini et al. 2006; Tominaga et al. 2006; Jagadeesh et al. 2011; Menezes et al. 2012; Rakesh et al. 2012).

Shock waves and radial pressure waves are successfully used worldwide to regenerate tissue by means of a complex physical and biological phenomenon referred to as *mechanotransduction* (Schaden et al. 2007; Wess et al. 2007; Wang et al. 2009d; Mittermayr et al. 2011, 2012; d'Agostino et al. 2015). Shock waves with an energy flux density (EFD) of about 0.1 mJ/mm^2 applied at a rate of 4 Hz have been proposed as an alternative to stem cell therapy for ischemic heart and limb disease (Tepeköylü et al. 2013). ESWT is given to patients suffering from chronic tendinopathies, especially when conservative treatments fail (Peers et al. 2003; Wang et al. 2007; Furia 2008; Rasmussen et al. 2008; van Leeuwen et al. 2009; Zwerver et al. 2010; Galasso et al. 2012; Moya and Patiño 2012; Al-Abbad and Simon 2013; Furia et al. 2013; van der Worp et al. 2013; Gerdesmeyer et al. 2015a). Some applications of shock and radial pressure waves to ailments, such as wound healing disorders (Schaden et al. 2007; Dumfarth et al. 2008; Qureshi et al. 2011; Wolff et al. 2011; Contaldo et al. 2012; Mittermayr et al. 2012; Ottomann et al. 2012; Dymarek et al. 2014; Notarnicola et al. 2014), ischemic heart disease

(Zimpfer et al. 2009; Ito et al. 2011; Shimokawa and Ito 2010; Schmid 2014), spasticity (Vidal et al. 2011; Gonkova et al. 2013; Kim et al. 2013; Moon et al. 2013; Lohse-Busch 2014; Santamato et al. 2014), musculoskeletal disorders of fascial origin (Legat 2014), myofascial pain (Gleitz 2011; Jeon et al. 2012; Legat 2014; Ramon et al. 2015a), osteoarthritis (Wang et al. 2012c; Zhao et al. 2012), osteoporosis (van der Jagt et al. 2009; d'Agostino et al. 2011; Gerdesmeyer et al. 2015b), the bone marrow edema syndrome (d'Agostino et al. 2014; Gao et al. 2015), *osteochondritis dissecans* of the knee and the talus (Thiele et al. 2015b), medial tibial stress syndrome (Rompe et al. 2010), the Peyronie's disease (Butz and Teichert 1998; Kiyota et al. 2002; Lebret et al. 2002; Skolarikos et al. 2005; Palmieri et al. 2009; El-Husseiny et al. 2010b), and erectile dysfunction (Gruenwald et al. 2012, 2013; Lei et al. 2013; Abu-Ghanem et al. 2014; Reisman et al. 2015; Srini et al. 2015) may become more popular in the near future and eventually substitute conventional treatment modalities. Shock waves have proven effectiveness in bone conditions, such as avascular necrosis, delayed unions (slow-healing bone), non-unions (non-healing bone), and stress fractures (Schaden et al. 2001; Durst et al. 2002; Wang et al. 2005, 2015a; Lin et al. 2006; Liu et al. 2006; Leal et al. 2007, 2015; Alves et al. 2009; Elster et al. 2010; Furia et al. 2010a, b; Vulpiani et al. 2012; Russo 2014; Kuo et al. 2015; Russo et al. 2015). The use of shock waves and radial pressure waves is increasing rapidly, especially in the management of pain, such as the treatment of the greater *trochanteric pain syndrome* (inflammation of a part of the hip) (Del Buono et al. 2012) and *coccydynia* (coccyx pain) (Marwan et al. 2014). Furthermore, ESWT is widely used to treat *calcaneodynia* (heel pain), *scapulohumeral periarthritis* (inflammation of the tendons of the shoulder), *radiohumeral bursitis* (tennis elbow), soft tissue inflammation, diabetic foot, and non-healing wounds (Angehrn et al. 2007; Chow and Cheing 2007; Wang et al. 2011a, 2015b; Wilson and Stacy 2011; Goertz et al. 2012, 2014; Silk et al. 2012; Rompe et al. 2015). rESWT has been used successfully to reduce soft tissue pain syndromes after total knee arthroplasty (Gerdesmeyer and Krath 2014). The use of radial pressure waves to treat patients suffering from *calcaneal apophysitis*, a painful inflammation of the heel's growth plate that affects children between about eight and 14 years of age, also seems to be a promising therapy (Nauck et al. 2014). The possible use of shock waves to reduce tooth mobility and rehabilitate adjacent tissues is another example of the wide range of applications of ESWT (Falkensammer et al. 2014, 2015).

As will be described, relatively high-energy flux densities are used for pathological calcifications, delayed unions, and avascular necrosis. More sensitive tissues like tendons are treated with lower energies. In contrast to SWL, the success of ESWT is more difficult to evaluate. A common measure of ESWT outcome is pain relief; however, pain is a subjective measure, sometimes determined using the visual analogue scale (VAS) (Scott and Huskisson 1976). Pre- and post-treatment evaluation of the functional status is done using especially designed questionnaires. Even if there are many articles reporting positive treatment outcomes, in several applications evidence is still inconclusive in regard to the effectiveness of ESWT.

This is mainly due to short or different follow-up times, deficient study descriptions, inappropriate statistical analysis, small sample sizes, different parameters used, different shock wave or radial pressure wave sources used, subjective scores, and lack of treatment blinding. In most applications, more research is necessary to define the optimal therapy dose. For instance, evaluation of ESWT to treat tendinopathies by comparing clinical results has been complicated and controversial, because publications report different shock wave sources, energy settings, treatment protocols, and evaluation methodologies (Thomson et al. 2005; Lee et al. 2011; Zwerver et al. 2011; Galasso et al. 2012).

A therapy protocol should at least include the EFD, the number of shock or radial pressure waves, information on the pressure profile, the pressure pulse rate, the model and manufacturer of the device used, the intensity level, the coupling method and medium, as well as the number of sessions and the interval between treatments. Unfortunately, so far there is no reliable physical pressure wave parameter, such as the EFD or the focal volume, which is related to biological effects and clinical outcomes in a direct and easy way. Moreover, the reported EFD and pressure profile values may have been obtained using different methodologies. This should be considered when comparing treatment protocols, data published in scientific articles, or specifications provided by manufacturers. So far, there is no consensus on the optimal number of sessions, pressure wave dose, energy level, and application rate. This is even more complicated for ballistic devices, because most parameters defined in the International Electrotechnical Commission (IEC) standard 61846 only refer to the focal point.

This chapter does not cover all applications of ESWT and radial pressure wave therapy. Due to the huge amount of published information, only a brief discussion of some studies is given in each section. Today, there is an increasing variety of ESWT devices on the market. Only few representative systems could be included.

Before using clinical ESWT devices, it is strongly recommended to verify if they meet the standards of the International Society for Medical Shockwave Therapy (ISMST). Detailed technical information, quality control, and well-designed and scientifically conducted research are mandatory before clinical use (Ramon et al. 2015b). Collaboration between medical societies may be helpful to avoid the use of methods and equipment that have not been verified properly. Shock waves and radial pressure waves should always be administered by well-trained personnel. Certification must involve thorough theoretical and practical instruction by experts in the field, and should not be substituted by short courses.

Due to its noninvasive approach and minimal side effects, the future of ESWT is promising and novel applications of shock waves and radial pressure waves will arise in fields, such as orthopedic and regenerative medicine, tissue engineering, and cell therapy (Romeo et al. 2014; d'Agostino et al. 2015). The fast development of *mechanobiology*, a science that combines physics and biology will contribute to this (Jansen et al. 2015).

6.2 Focused, Defocused, and Planar Pressure Wave Sources

So far there is no evidence that a certain shock wave generation principle (electrohydraulic, electromagnetic, or piezoelectric) is superior for ESWT (Schmitz et al. 2015). Depending on the specific application, focused, defocused, or planar shock waves are used (Fig. 6.1). Similar to extracorporeal lithotripters, focused shock wave sources for ESWT concentrate the energy generated by electrohydraulic (Fig. 6.2), electromagnetic, or piezoelectric devices on a small tissue volume. The penetration depth, the focal volume, and the EFD may be adjusted and vary from one manufacturer to another. Cylindrical electromagnetic shock wave sources with a parabolic reflector and in-line localization are standard in some ESWT devices. To avoid damage to the surrounding tissue, for therapies that require high-energy densities, accurate localization of the region to be treated, using radiographic or ultrasound imaging, is crucial. There are devices that include co-axially arranged

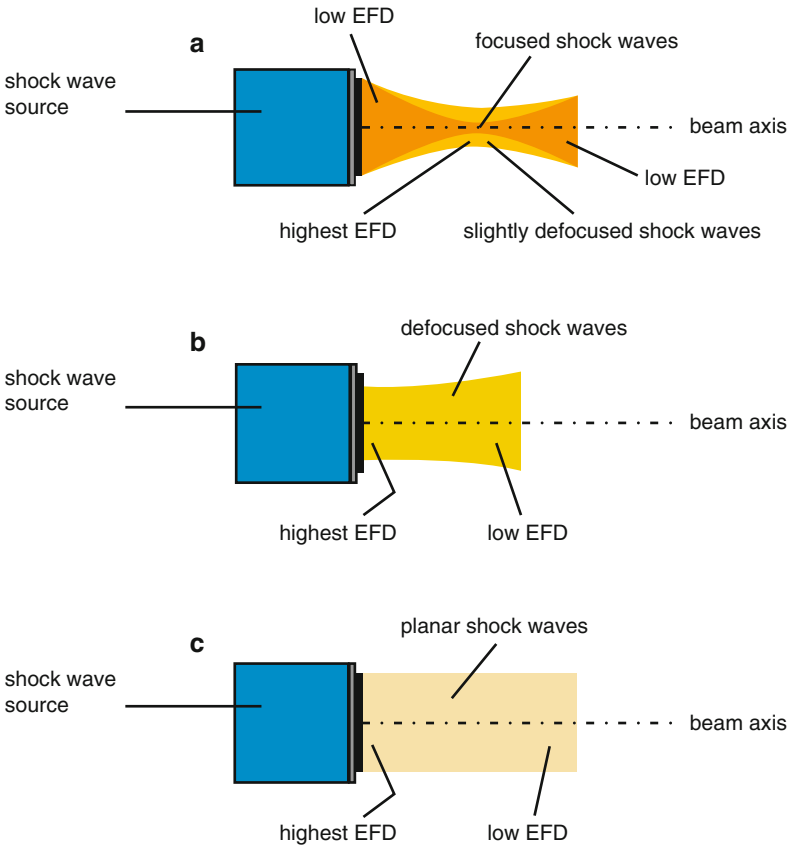


Fig. 6.1 Sketch of (**a**) a focused and a slightly defocused pressure wave beam, (**b**) a defocused beam, and (**c**) a plane beam

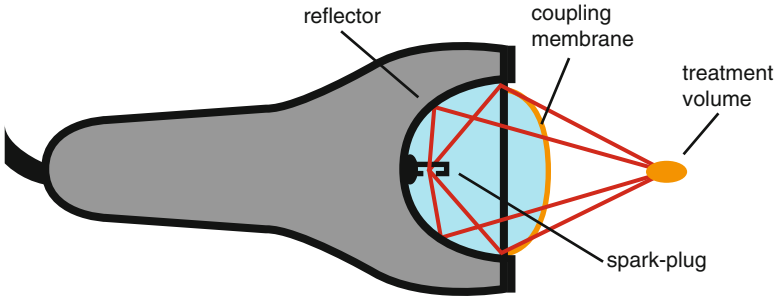


Fig. 6.2 Hand-held electrohydraulic shock wave source for extracorporeal shock wave therapy. Energy concentration depends on the shape of the reflector

Fig. 6.3 Photograph of the *Epos Ultra* (Dornier MedTech GmbH, Wessling, Germany) electromagnetic shock wave source during treatment of plantar fasciitis, showing (*1*) the coupling cushion of the shock wave source, attached to an articulated arm, and (*2*) the ultrasound scanner

(in-line) imaging modalities while other manufacturers designed systems where the transducer is outside the shock wave source (off-line configuration). Some shock wave sources for ESWT use cushions similar to those of extracorporeal lithotripters to couple the acoustic waves into the body. A potential advantage of focused shock wave sources is that the maximum energy can be concentrated deep inside the body. Depending on the specific application, large aperture angles of the shock wave source could be desirable to provide low-energy density at the coupling area and generate less pain. Focused shock wave sources as used for ESWT can have a penetration depth of up to 200 mm (Mittermayr et al. 2012; Dymarek et al. 2014; Novak 2014; Speed 2014).

Several ESWT devices are inspired in extracorporeal lithotripters. An example is the *Epos Ultra* (Dornier MedTech GmbH, Wessling, Germany), a flat coil electromagnetic shock wave source (Sect. 5.3.1) with a 5.5 inch aperture (Fig. 6.3). According to the in-house measurements performed by Dornier, the EFD and the peak-positive pressure can be varied from 0.13 to 1.7 mJ/mm^2 and about 7.5 to 80 MPa, respectively. The penetration depth is approximately 76 mm. The system can operate

at a shock wave rate of up to 4 Hz. Ultrasound imaging allows precise localization of the treatment zone.

Some extracorporeal lithotripters can be used for ESWT (Fig. 6.4); however, many shock wave generators for shock wave therapy are table top devices without ultrasound or X-ray monitoring. The *Aries* (Dornier MedTech GmbH), shown in Fig. 6.5, has a flat coil electromagnetic shock wave source (Sect. 5.3.1). The system, integrated in a lightweight therapy head for hand-held operation, is significantly smaller (aperture approximately 40 mm) than SWL sources. Being designed to target regions which are superficial or at shallow penetration depth, it has a fixed focus which is close to the therapy head surface (Fig. 6.6). The energy flux density (EFD) can be varied from approximately 0.01–0.31 mJ/mm^2. No anesthesia is required during therapy with this device. A model to be used in veterinary medicine (*Aries Vet*) is also available.

The *Piezoson 100 plus* (Richard Wolf GmbH, Knittlingen, Germany) has been a representative device for ESWT. It was designed for several indications, such as jumper's knee, plantar fasciitis (PF), pseudoarthrosis, tendinosis calcarea, and tennis elbow.

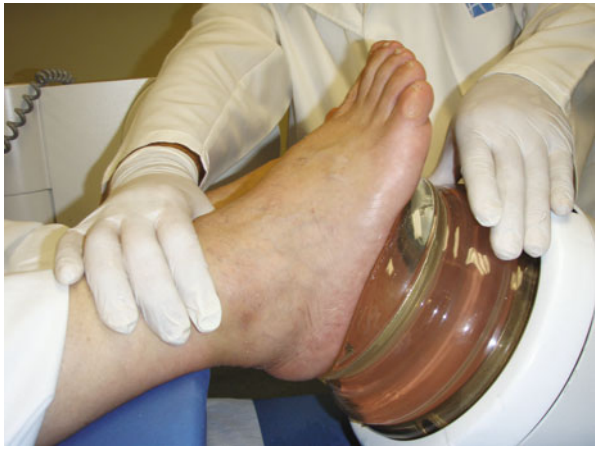


Fig. 6.4 Some lithotripters such as the *Compact Sigma* (Dornier MedTech GmbH, Wessling, Germany) may be used to perform extracorporeal shock wave therapy

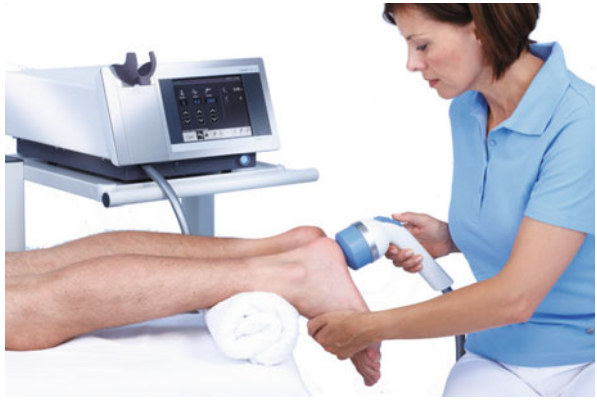


Fig. 6.5 The *Aries* electromagnetic shock wave therapy device during treatment of plantar fasciitis. (Courtesy of Dornier MedTech GmbH, Wessling, Germany)

Fig. 6.6 Image of the *Aries* shock wave source showing the geometry of different isobars of the focal zone. The penetration depth can be varied by modifying the energy settings. As the energy rises, the 5 MPa isobar intersects the beam axis at a larger distance from the therapy head. (Courtesy of Dornier MedTech GmbH, Wessling, Germany)

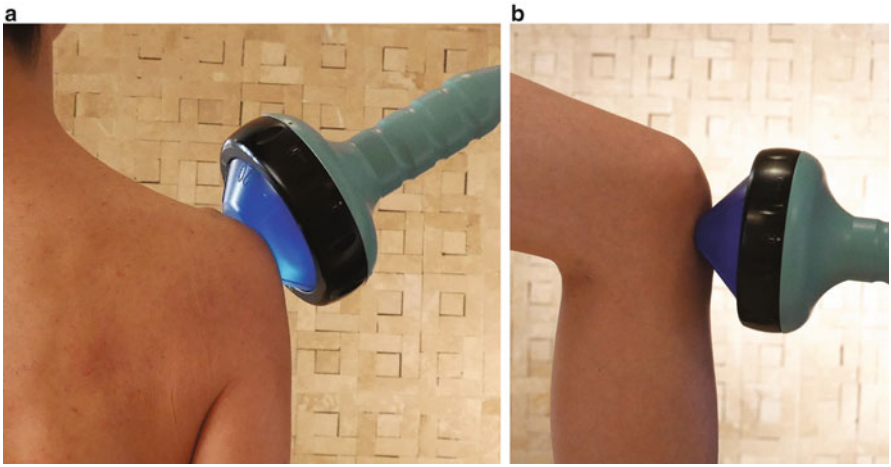


Fig. 6.7 The *FB10G4* shock wave source of a *Piezoson 100 plus* (Richard Wolf GmbH, Knittlingen, Germany) (**a**) during soft tissue therapy at the rotator cuff of the shoulder, and (**b**) during treatment of the patellar tendon attachment

The operation of its *FB10G4* shock wave source, shown in Fig. 6.7 (diameter 100 mm), is similar to the shock wave head of the *Piezolith 3000* lithotripter described in Sect. 5.4.1 (Fig. 5.58). To facilitate therapy to a wide variety of clinical cases, the system has several energy levels. The control and display unit is small and simple to operate. An interesting feature of the device are gel-filled waterless therapy coupling elements that can be changed easily (Fig. 6.8). The different heights of the cone-shaped gel pads allow treatment at different penetration depths in increments of 5 mm. The penetration range depends on the model of the shock wave source connected to the control unit. The so-called trigger point shock wave therapy (TPST) is also possible due to the small focus of the shock wave source. The shock wave rate can be increased up to 8 Hz. The approximate EFD and peak-positive pressure depend on the shock wave source and the selected intensity and can be varied from approximately 0.03 to 1.1 mJ/mm^2 and from 11 to 126 MPa, respectively.

Fig. 6.8 Photograph of three of the six gel pads that can be used with the *FB10G4* shock wave source of a *Piezoson 100 plus* (Richard Wolf GmbH, Knittlingen, Germany)

The current model manufactured by Richard Wolf GmbH, named *PiezoWave2*, also uses piezoelectric shock wave generation. Depending on the required energy, either single-layer shock wave sources (*F7G3* with a 70 mm aperture and 30 mm maximum penetration depth or *F10G4* with a 100 mm aperture and 40 mm maximum penetration depth) or double-layer shock wave sources (*FB10G4* with a 100 mm aperture and 40 mm maximum penetration depth or *FB10G*6 with a 100 mm aperture and 60 mm maximum penetration depth) can be used. For instance, for the *F10G4* single-layer shock wave source coupled to the *PiezoWave2* control unit, the peak-positive pressure reported by the manufacturer is approximately 78 MPa and the maximum EFD reaches about 0.8 mJ/mm^2. The approximate values obtained for the *PiezoWave2*/*FB10G6* combination are $p^+ = 76$ MPa and EFD = 0.7 mJ/mm^2. Interchangeable coupling pads, as described for the *Piezoson 100 plus*, are available to vary the penetration depth with all shock wave sources (Fig. 6.9).

Linear focusing dual-layer (Fig. 6.10) and planar radiating pressure wave sources are also available for this system; however, neither one of them generates a shock wave. An elongated *treatment volume* is generated with the linear focusing transducer model *FBL10×5G2*. In this case, two layers of piezoelectric elements are arranged on the sector of a cylindrical backing surface. As in other piezoelectric shock wave sources, pressure pulses are generated by extremely fast and small elongations of the elements. According to the manufacturer, the rise time of the pressure pulse generated by the *FBL10×5G2* is about 0.5 µs. Special gel pads are also used with this transducer to adjust the penetration depth between 0 and 20 mm. The majority of acute and chronic pain syndromes of the musculoskeletal system can be treated by selecting the appropriate transducer of the *PiezoWave2*.

A linear electromagnetic pressure wave source called *Renova* was introduced to the market by Direx Systems Corporation (Canton MA, USA). According to the manufacturer, the device has the advantage that it enables focusing shock waves on

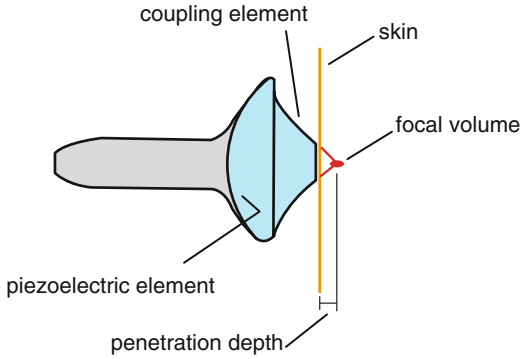
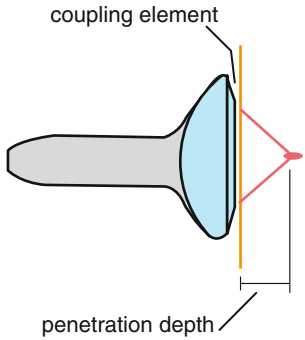


Fig. 6.9 Sketch of a *F10G4* piezoelectric therapy source as used in the *PiezoWave2* (Richard Wolf GmbH, Knittlingen, Germany) with two different coupling elements to achieve superficial and deep shock wave penetration



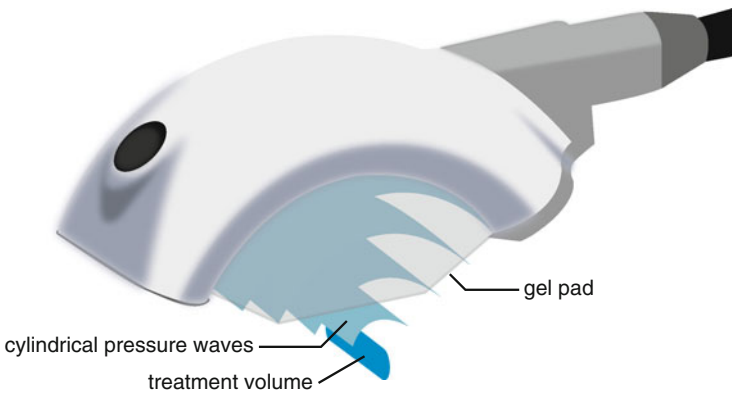


Fig. 6.10 Schematic of an *FBL10×5G2* double-layer piezoelectric linear shock wave therapy source as used in the *PiezoWave2* (Courtesy of Richard Wolf GmbH, Knittlingen, Germany)

a 70 mm long and 10 mm width treatment region. Pressure pulses can be emitted at 5 Hz. It was designed to induce local angiogenesis to improve the penile hemodynamics in patients suffering from ED. No precise information on the generated pressure field is available so far.

Compact electrohydraulic shock wave sources consisting of a half-ellipsoidal brass reflector with an opening diameter of only 20 mm have also been developed (Hosseini et al. 2006, 2011; Oshita et al. 2014). As in the larger shock wave sources described in Sect. 5.2.1, electrodes were placed at the first focal point (*F1*) of the reflector. Shock waves were produced by an electric discharge at *F1*, reflected off the reflector and focused towards *F2*. An interesting feature of the device is that its focal zone is at least one order of magnitude smaller than the focal zone of extracorporeal lithotripters. Potential applications are the treatment of pain or its use in cardiology. The authors studied the characteristics of both the shock wave generated by the plasma expansion and that produced by the plasma bubble collapse at *F1*. Measurements at *F2* revealed that the shock wave produced by the plasma expansion was much stronger than the second shock wave generated due to bubble collapse. Okuda et al. (2011) proposed the use of compact electrohydraulic shock wave sources for cranioplasty, i.e., the repair of a bone defect in the skull after surgery or injury.

Planar and defocused shock waves are useful to treat relatively large tissue regions per shock wave. As a consequence, the EFD is reduced because the total energy remains the same. Medical devices similar to the spark-gap shock wave source shown in Fig. 6.2, but equipped with small parabolic instead of ellipsoidal reflectors, that fit into the hand-piece of an ESWT device are manufactured by several companies. These systems are used to treat superficial lesions like cutaneous ulcers where a low penetration depth is desirable (Mittermayr et al. 2012). Planar waves deliver relatively low energy into soft tissues at a large area (approximately 30–50 mm^2) (Notarnicola et al. 2012).

The previously described *PiezoWave2* control unit (Richard Wolf GmbH) can be equipped with a planar pressure wave source (model *FP4*) as the one shown in Fig. 6.11. In this case, the piezoelectric elements are arranged on a circular plane

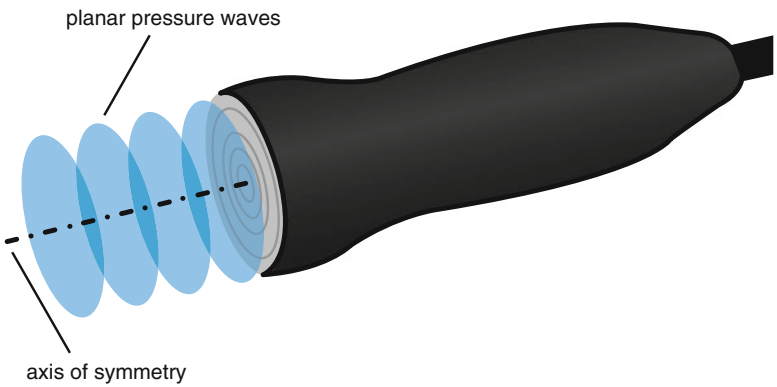


Fig. 6.11 Schematic of an *FP4* planar piezoelectric shock wave therapy source as used in the *PiezoWave2* (Courtesy of Richard Wolf GmbH, Knittlingen, Germany)

backing surface (40 mm in diameter) and a non-focused pressure wave is emitted at a rate between 1 and 8 Hz. According to the manufacturer, at a distance of 1 mm along the beam axis, p^+ and the EFD equal approximately 3 MPa and 0.06 mJ/mm^2, respectively. These in-house measurements were obtained with an FOPH hydrophone at one spot only, because for non-focusing devices it is not possible to follow the IEC 61846 international standard exactly. Emission of a true planar wave with a constant intensity within the whole cross section is impossible.

6.3 Ballistic Sources

As mentioned before, electrohydraulic, electromagnetic, and piezoelectric shock wave sources can be adapted or redesigned to be used not only for SWL but also for ESWT. A pressure wave source, which is not used in SWL, is the *ballistic* device. Ballistic pressure wave sources are often called *radial shock wave sources*; however, strictly speaking this is not correct, because ballistic sources do not generate shock waves (Sect. 3.2), even if they may generate acoustic cavitation (Cleveland et al. 2007; Császár et al. 2015). For ballistic sources to produce shock waves, the pressure output would have to be higher.

Because bioeffects are related to the pressure waveform, the therapeutic effects of radial pressure waves may differ from that of focused shock waves. A difference between focused shock wave sources and radial pressure wave sources is the propagation distance from the source to the target. Nevertheless, Schmitz et al. (2015) reported that there is no evidence in favor of either focused shock waves or radial pressure waves with respect to treatment outcomes for patients with patellar tendinopathy.

Radial pressure waves are applied by moving a hand-piece manually (Fig. 6.12). The physical principle is analogous to that used by pneumatic jackhammers. In radial pressure wave generators, compressed air accelerates a projectile (mass about 3 g) located inside a small cylindrical guiding tube of approximately 200 mm length to a speed of 5–25 m/s (Fig. 6.13). A pressure wave with a long positive pulse duration and an amplitude of up to 10 MPa (Fig. 3.11) is produced when the projectile hits an applicator at the end of the tube, displacing it less than a millimeter. The motion of the projectile is damped by an elastic ring located between the applicator and the hand-piece. At its outer surface the applicator can be flat, concave, or convex. This surface is placed in contact with the patient, distributing the pressure waves in a radial fashion. The EFD is highest at the skin surface, weakening as the wave penetrates the tissue. In most equipment several applicators are available to vary the penetration depth from approximately 0–60 mm (Mittermayr et al. 2012; Dymarek et al. 2014). Ultrasound gel or castor oil is used to couple the pressure pulses into the tissue; however, due to the large difference between the acoustic impedance of metal and tissue, only about 10 % of the energy is transmitted into the patient (Novak 2014). Pressure pulse coupling into the patient's body is challenging when using ballistic sources because the motion of the projectile results in recoil of the

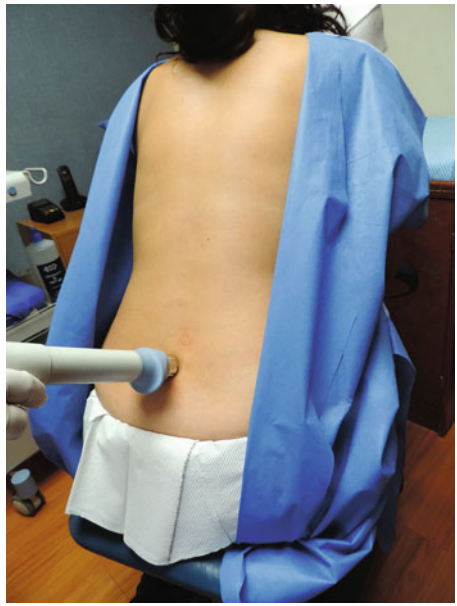


Fig. 6.12 Application of radial pressure waves to the paravertebral region of a patient suffering from muscular contracture using a *5000 SWT Power* unit (BTL Laboratorios de Tecnología, México). (Courtesy of J. Lozano Pardinas)

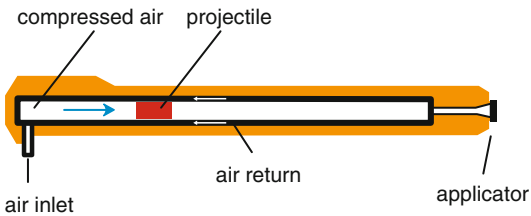


Fig. 6.13 Schematic of the hand-piece of a ballistic radial pressure wave source. Compressed air fires the projectile within a guiding tube. As the projectile hits the metallic applicator, stress waves are produced and transmitted into the patient's tissue

hand-piece, separating the applicator from the skin. Special care should be taken with some focused applicators, since their concave shape facilitates bubbles to get trapped between the applicator and the skin. Contrary to focused shock wave sources, in ballistic therapy heads the pressure and the EFD are highest at the surface of the applicator (Fig. 3.10). Consequently, deep tissues are difficult or impossible to be efficiently treated with radial pressure waves. The *Duolith SD1* (Storz Medical AG, Tägerwilen, Switzerland) was the first system to offer both focused shock waves and radial pressure waves.

When using ballistic therapy heads, it should be kept in mind that there is no linear relationship between the air compressor pressure and the energy output, and that two different models operating at the same air compressor pressure may not generate the same pressure field. More acoustic cavitation is to be expected when increasing the air pressure setting and, according to Császár et al. (2015), less cavitation

is produced operating the device at high frequency compared to low frequency. Furthermore, it is important to distinguish between the air compressor pressure (generally given in bar) and the pressure pulse amplitude generated by a ballistic device (generally given in MPa). For instance, the 5.5 MPa (55 bar) peak-positive pressure shown in Fig. 3.11 could have been generated by adjusting the air compressor pressure of the radial pressure wave generator at 3 bar. In this case, 55 bar is the pressure measured at a specific distance from the applicator and 3 bar is the required air pressure to produce the 55 bar output.

Because of differences in experimental setups there may be considerable discrepancies between pressure measurements reported in scientific publications and those reported by manufacturers. Perez et al. (2013) recorded the pressure waveforms emitted by a *Duolith SD1T-Top* (Storz Medical AG). According to their measurements, the waveform consists of a leading positive pulse ($p^+ = 8$ MPa) with a duration of 5 μs, followed by a negative phase with a p^- equal to about −5.7 MPa. The reported EFD is 0.115 mJ/mm^2 and most of the energy is contained at or below 200 kHz. Cleveland et al. (2007) carried out pressure measurements on a *DolorClast Vet* (Electro Medical Systems, Nyon, Switzerland) ballistic pressure wave source. The pressure waves generated by this equipment were transmitted into a small water tank through a membrane and recorded with a polyvinylidenevfluoride (PVDF) hydrophone and an in-line preamplifier. A convex shaped applicator with a 15-mm diameter, referred to as unfocused applicator and a focused concave applicator with a 12-mm diameter were tested. Adjusting the air compressor pressure at 3 bar, the waveform at 10 mm from the unfocused applicator consisted of a positive pulse with p^+ equal to 5.6 MPa and a 3.8 μs t_{FWHMp+} duration (Fig. 3.1), followed by a strong negative phase ($p^- = -9.2$ MPa), demonstrating that, contrary to shock wave pressure waveforms, the amplitude of the negative phase of ballistic sources may be larger than the generated compressive pulse (Fig. 3.11). The pressure returned to the baseline after approximately 15 μs. The EFD (obtained by integrating the intensity from 0 to 25 μs) was 0.234 mJ/mm^2. The positive and negative phase produced by the focused applicator had a peak pressure of 3.4 MPa and −5.2 MPa, respectively. The t_{FWHMp+} duration of the positive pulse lasted 3.4 μs and the calculated EFD was 0.158 mJ/mm^2. With the *DolorClast Vet*, the highest p^+ obtained was 8 MPa. The negative phase was always followed by a complex tail. According to the authors, this equipment does not generate shock waves, i.e., none of the waveforms had a shock front. For all settings, the rise times were too long for the pulse to be a shock wave. The −6 dB focal zone was a region extending 40 and 20 mm from the tip of the device for the unfocused and the focused applicator, respectively.

Császár et al. (2015) used several techniques to compare the pressure field of two radial pressure wave equipment (*D-Actor 200*, Storz Medical AG, and *DolorClast*, Electro Medical Systems) and a vibrating massage device (*Vibracare*, General Physiotherapy, Inc., St. Louis, MO, USA) that generates vibrations by means of a rotating flywheel mass. The authors concluded that cavitation may be generated in rESWT devices but does not occur in vibrating systems. Cavitation may induce desired therapeutic bioeffects, but may also cause negative effects on the body (Wan et al. 2015). Because rESWT systems generate cavitation, there are contraindications to target areas located above air-filled tissues, while some vibrating devices may be used for respiratory therapy applications.

The *Masterplus MP 100*, manufactured by Storz Medical AG is a modern ballistic radial pressure wave source (Fig. 6.14). Although the manufacturer refers to the system as a radial shock wave therapy device, strictly speaking it does not emit shock waves. For convenience, the number of pulses, the frequency, and the energy can be selected on the hand-piece. Preset parameters recommended by experts for specific indications may be chosen. Furthermore, step-by-step protocols for a variety of therapies are available via the Internet, guiding the physician according to the latest clinical reports. Another feature is several selectable pressure pulse applicators (Fig. 6.15) for acupuncture, gel-free coupling, calcified tendonitis of the

Fig. 6.14 Photograph of the Storz *Masterplus MP 100*, showing (*1*) the radial pressure wave hand-piece, (*2*) the pressure pulse transmitter, (*3*) the control display, (*4*) the vibration therapy head, and (*5*) the power module with built-in air compressor. (Courtesy of Storz Medical AG, Tägerwilen, Switzerland)

Fig. 6.15 Photograph of radial pressure wave transmitters for a *Masterplus MP 100*. (Courtesy of Storz Medical AG, Tägerwilen, Switzerland)

shoulder, humeral epicondylitis, patellar tendonitis, and PF. The diameters of the transmitters range from 6 to 35 mm. Available frequencies are 12, 16, and 21 Hz. The air compressor pressure of the device can be varied between 1.0 and 5.0 bar. At a distance of 2 mm, the EFD of the *Masterplus MP 100* ranges between 0.05 and 0.28 mJ/mm^2, and the peak-positive pressure (p^+) at the minimum and maximum air pressure setting is approximately 4.9 and 18.5 MPa, respectively. The corresponding peak-negative pressure (p^-) is −3.5 and −3.7 MPa, and the rise time of the positive pressure pulse (t_r) is approximately 3 µs. These in-house pressure values were obtained using a PVDF needle hydrophone. A vibration therapy unit can be connected to the *Masterplus MP 100* as an optional item. It operates at frequencies of up to 31 Hz and may be used for therapies different to those indicated for the radial pressure wave source.

It is crucial to know the fundamental differences between focused shock waves, radial pressure waves, and vibrations as used for massage, to select a safe and effective treatment protocol according to each case. Focused shock waves and radial pressure waves may complement each other and could be used in combination (Gleitz 2011). While radial pressure waves are suitable for the treatment of large areas, focused shock waves are designed to treat local spots (Fig. 3.10).

6.4 Other Shock Wave Sources for ESWT

A different method to generate high-amplitude pressure pulses in liquids for biomedical applications was designed a few years ago (Dion et al. 2012). The device consists of an aluminum cylindrical waveguide (diameter 25 mm, length 600 mm) with a piezoelectric transducer (diameter 28 mm, central frequency 600 kHz) attached at one side. A two-layer epoxy-glass acoustic coupler was fixed at the other end of the waveguide to match its acoustic impedance to that of water. Pressure pulses of more than 10 MPa may be generated by immersing the end of the shock wave source in water. Interesting advantages of the device are that the pressure profile can be modified to a certain extent through software control and that the device is relatively simple and inexpensive.

Hosseini et al. (2006) developed a small microexplosive shock wave source to study the response of cells after shock wave exposure. In another study, interesting approaches to cardiovascular therapy, cancer treatment, and cranioplasty in close vicinity of the brain were considered. The system consisted of a half-ellipsoidal metallic reflector with a 20 mm opening diameter. To produce a shock wave, a silver azide pellet (between 1 and 20 mg) placed at the focus (*F1*) closest to the reflector was ignited by irradiation of a Q-switched Nd:YAG laser beam (Hosseini et al. 2005).

For some procedures, such as revascularization therapy and neurosurgery (Sect. 7.3), precise shock wave focusing is needed. Hosseini and Takayama (2004) studied the generation of spherical shock waves and cavitation in water using a

Q-switched holmium:yttrium aluminum garnet (Ho:YAG) laser (pulse duration 200 ns, wavelength 2.1 μm) and double exposure holographic interferometry. Compared to shock wave sources as used in SWL, a two order of magnitude reduction in the focusing area was achieved. Sequential infinite fringe interferograms of shock wave generation and propagation from the tip of an optical fiber were obtained. The laser heated the liquid at the fiber tip, producing a small fast-expanding plasma bubble that radiated a spherical shock wave.

6.5 Pain Relief

The main goal of several therapies described in the remaining part of this chapter is pain relief. Chronic pain is one of the most frequent diseases, regardless of many treatment modalities. Hundreds to a few thousand shock waves, at a rate between 1 and 4 Hz with about one tenth of the energy used in SWL, are normally applied to treat chronic pain. The therapy is divided into several sessions with a rest between treatments of days or weeks. Even if no pressure field parameter has been identified to be directly related to clinical outcomes, it seems reasonable to believe that the EFD (Sect. 3.5) influences pain relieving processes. Candidates for ESWT are patients in whom the pain has lasted for several months without responding to conservative therapies, such as massage, exercises, cortisone injections, and anti-inflammatory medications. Shock and radial pressure waves should not be applied close to air-filled cavities, infected zones, bone tumors, and patients with certain circulation or nerve disorders. ESWT is contraindicated for pregnant patients.

Different theories have been proposed as pain relief mechanisms after ESWT and rESWT. Some authors report that the therapy seems to stimulate the nociceptors to fire impulses and that the propagation of nerve impulses is blocked according to the gate-control theory. Another possibility is that pain sensation is diminished because the pressure pulses alter cell membranes, so that the nociceptors cannot build up generator potentials. Furthermore, shock waves may produce free radicals in the neighborhood of cell membranes, resulting in pain-reducing chemicals close to the cells. Shock wave-enhanced revascularization is also believed to be a mechanism of pain relief. The mechanisms of cell apoptosis, improved angiogenesis (sprouting of capillaries from preexisting vessels), wound healing, and new bone formation induced by radial pressure waves have been reported by several authors (Contaldo et al. 2012; Zhao et al. 2012; Gollwitzer et al. 2013).

An interesting neural model for pain relief by extracorporeal shock wave treatment published by Wess in 2008 states that when acute pain develops into chronic pain, sensor input and motor output are stored in the peripheral nervous system and/or the central nervous system and act in a feedback circle, so that the cause of the pain shifts from the organ to another level of the nervous system. According to this, the treatment should erase the particular memory instead of modifying the organ itself.

6.6 Plantar Fasciitis

Plantar fasciitis (PF), also called *plantar fasciosis*, is a musculoskeletal disorder that results from repeated trauma, described by pain in the plantar fascia, a tendon attached to the heel bone which runs from the heel to the toes. Up to 15 % of people develop PF throughout their life (Thomas et al. 2010). Histologic findings by Lemont et al. (2003) revealed that PF is a degenerative *fasciosis* without inflammation and not a *fasciitis*. According to this, the correct term would be *plantar fasciopathy* (Rompe 2009; Schmitz et al. 2013). Even if its multi-factorial etiology is still not completely understood, more than 90 % of the patients with PF are cured with non-surgical therapies within 6 months. Obesity, occupations that require prolonged weight-bearing, and reduced ankle dorsiflexion are risk factors associated with PF (Roxas 2005). Rest, application of ice, physiotherapy, and analgesic medication are conservative therapies. Heel cups are sometimes used to absorb the impact of walking. Alternatives also include local radiofrequency ablation and ultrasound. If the pain persists, nonsteroidal anti-inflammatory drugs or a local injection of steroids may be helpful; however, in general the improvement is slow and the use of corticoids is debated (Hsiao et al. 2015). Surgery may be needed in patients with severe symptoms; however, at the present time shock wave therapy is considered as the best treatment modality (Gollwitzer et al. 2007; Gerdesmeyer et al. 2008, 2015b; Piontkowski et al. 2010).

The use of extracorporeal shock waves to treat patients suffering from PF was first published in the mid-1990s (Dahmen et al. 1995) and in 2001 radial pressure waves were introduced for the treatment of this injury (Schöll and Lohrer 2001). Several reports on ESWT to treat proximal PF followed (Rompe et al. 2002, 2003; Ogden et al. 2004; Norris et al. 2005; Roxas 2005; Wang et al. 2006; Gollwitzer et al. 2007; Gerdesmeyer et al. 2008; Chuckpaiwong et al. 2009; Ibrahim et al. 2010; Metzner et al. 2010; Aqil et al. 2013). The FDA approved ESWT for PF in 2000. It is considered as an option for cases that are resistant to conventional treatments. The American College of Foot and Ankle Surgeons suggests that before surgery or ESWT, patients should have chronic symptoms and undergo conservative treatment for at least 6 months (Thomas et al. 2010).

During ESWT, shock waves are directed at the plantar fascia (Fig. 6.4), reducing inflammation and pain from the affected ligament; however, the benefits may take 3 months or more to be fully effective. Ultrasound may be used to position the shock wave source adequately. Local anesthesia is sometimes administered; however, there is evidence that local anesthesia reduces the effectiveness of ESWT to treat chronic PF (Labek et al. 2005).

There are essentially three modalities reported to treat PF: ESWT performed at shock wave energy densities equal to or lower than 0.12 mJ/mm^2, ESWT performed at energy densities higher than 0.12 mJ/mm^2, and radial pressure wave therapy. Sessions of 1000 pressure pulses with an EFD of 0.06 mJ/mm^2 applied three times per week resulted to be a successful therapy (Rompe et al. 2002). Kudo and colleagues (2006) reported ESWT with an *Epos Ultra* (Dornier MedTech GmbH)

on 114 patients suffering from PF. Previous conservative therapies were ineffective in all patients. Half of the patients were treated with one ESWT session, while the remaining group received placebo. A significant improvement in pain could be observed after 3 months in the ESWT treated patients. The visual analogue scale (VAS) and the Roles and Maudsley scores (Roles and Maudsley 1972) were used to evaluate therapy outcomes. In another study, comparing the results of about 80 single shock wave therapies using an *OssaTron* (High Medical Technologies, AG, Lengwil, Switzerland) for PF with a similar amount of conservative treatments, Wang and coworkers (2006) reported an approximately 69 % excellent, 14 % good, 6 % fair, and 11 % poor outcome for shock wave-treated patients, and 0 % excellent, 55 % good, 36 % fair, and 9 % poor outcome for the conservative treatment. Furthermore, ESWT patients had a recurrence rate of 11 %, while the control group had a recurrence rate of 55 %. A randomized controlled trial of 245 patients performed by Gerdesmeyer and colleagues (2008), comparing rESWT and placebo treatment for chronic PF revealed that radial pressure waves significantly improve pain and quality of life. Evaluation was based on the VAS and self-reports. Another promising study was published by Ibrahim et al. (2010). Their prospective, randomized analysis compared rESWT and placebo treatment for chronic PF. The main conclusion was that rESWT can reduce pain after two sessions.

Lohrer et al. (2010) compared radial pressure pulses (0.17 mJ/mm^2) with focused shock waves (0.20 mJ/mm^2) to treat PF using functional measures in a single-center parallel group design. Patients were randomized to either radial pressure waves or shock waves. Both treatment modalities were applied with a *Duolith SD1* (Storz Medical AG) in three sessions (2000 pulses per session) with 1 week interval. The foot function index (FFI) score, consisting of a pain scale which is composed of specific pain questions (Budiman-Mak et al. 1991) and neuromuscular performance tests, was used to determine therapy outcome. Analysis of all tested variables revealed better treatment outcomes in the shock wave-treated group compared to the radial pressure wave group; however, the authors admitted that the small number of patients ($n=39$) leaded to large confidence intervals of the single outcome variables with corresponding imprecision of the univariate results. Metzner et al. (2010) investigated results of ESWT to 63 patients that had PF for more than 6 months and failure of all non-surgical options for more than 3 months. ESWT was performed on an electromagnetic *Lithotripter S* (Dornier MedTech GmbH). One thousand shock waves (EFD=0.35 mJ/mm^2) were applied at a rate of 2 Hz. A 30 % VAS reduction was reported by 81 % and 96 % of the patients 6 weeks and an average of 73 months after ESWT, respectively (18 patients were lost to final follow-up). Because there was no control group it was not possible to evaluate the natural course of the disease. Definite conclusions on the long-term influence of the shock wave treatment could not be made.

Chang and colleagues (2012) reviewed several databases to compare the effectiveness of focused shock waves and radial pressure waves for managing PF. The authors concluded that rESWT is an appropriate alternative and may have a better effectiveness than focused shock wave therapy. Nevertheless, according to their meta-analysis, medium and high-intensity focused shock waves had a higher

success rate than the placebo treatments. This could not be affirmed for low-energy treatments because of the large confidence intervals.

A meta-analysis published in 2013 assessed the effectiveness of ESWT versus placebo in the treatment of PF (Li et al. 2013). The results revealed that ESWT was effective in treating patients suffering from recalcitrant PF, compared with patients receiving placebo therapy. According to their analysis, approximately 47–63 % of the ESWT patients achieved clinical success after 12 weeks follow-up. Their study also provided evidence that ESWT is not more effective compared with traditional treatments.

According to a study performed by Rompe and coworkers (2015), stretching exercises in combination with radial shock wave therapy is more efficient for the treatment of chronic symptoms of proximal plantar fasciopathy than repetitive radial pressure wave therapy alone. Patients were subjected to three sessions of 2000 radial pressure pulses (EFD = 0.16 mJ/mm^2) in weekly intervals, generated with a ballistic device (air compressor pressure 4 bar; rate 8 Hz) manufactured by Electro Medical Systems.

The costs of ESWT are much lower than those of surgery (open, percutaneous or endoscopic) and, according to a review of randomized controlled trials reported by Weil (2011), ESWT is commonly accepted as an alternative for the treatment of chronic PF. However, even if the majority of publications conclude that ESWT is a safe and efficient modality; there are also studies reporting that ESWT is ineffective to treat PF (Buchbinder et al. 2002; Haake et al. 2003; Speed et al. 2003). A meta-analysis by Thomson and colleagues (2005), that included almost 900 patients, was statistically significant in favor of ESWT for the treatment of PF pain; however, a sensitivity analysis including only high quality trials did not reveal a significant effect. Many specialists recommend ESWT to be used prior to last-line surgical treatment. Different treatment protocols, patient selection criteria, and devices used are the most probable causes of the reported discrepancies.

A double-blind randomized controlled trial on 25 patients with chronic PF to evaluate the efficacy of ESWT was reported by Marks et al. (2008). The main outcome measure of their study was the assessment of pain by means of the VAS and the Roles and Maudsley Score. The placebo group included nine patients and the ESWT group 16 patients. rESWT was applied using a ballistic *DolorClast* radial pressure wave generator (Electro Medical Systems) at an EFD of 0.16 mJ/mm^2 (air compressor pressure 2.5 bar). Patients in the rESWT group received 500 pressure waves during the first session and 2000 pulses in two following therapies at 3 day intervals. Sham treatment consisted in the same protocol as for patients in the rESWT group but using an EFD close to zero. After analyzing the results, the authors found a decrease in the VAS of over 50 % 6 months after the last therapy, compared with the VAS values before the trial in both the sham and the radial pressure wave group. There was no significant difference between the two groups, indicating that the placebo effect was the most important independent factor influencing treatment outcomes. An analysis of 11 clinical studies performed between 2002 and 2010 (Dizon et al. 2013) revealed that ESWT was more effective in improving functional outcome and in reducing morning pain compared to the placebo control

groups; however, in reducing overall pain no difference between the ESWT and the control groups was distinguished. Grecco et al. (2013) performed a randomized, prospective, comparative clinical study on 40 patients with a diagnosis of PF to compare treatment outcomes of radial pressure pulse therapy with conventional physiotherapy, and concluded that radial pressure pulse treatment was not more effective than conventional treatment 12 months after the last therapy. These results should not be generalized for all ESWT treatment modalities. As in most studies reporting results on ESWT, heterogeneity between the results occurs because of differences in the therapy protocols and the clinical devices used.

6.7 Calcaneal Spur

A *calcaneal spur*, also called *heel spur*, is the formation of an *osteophyte* on the heel bone, i.e., a calcium deposit on the bottom of the heel bone. It may appear when a foot is exposed to repeated stress, because calcium deposits pile up on each other, causing a painful deformity. More susceptible to form calcaneal spurs are women who wear high-heeled shoes, flatfooted or obese persons, and people standing long hours, frequently running in shoes with a hard sole or practicing certain sports that put intense tension on the feet (Frey and Zamora 2007). Physical therapy, overload reduction, pharmacotherapy, or surgery are standard treatments. Unfortunately, spurs may be recurrent.

Cosentino et al. (2001) studied the efficacy of ESWT in 60 patients who had pain associated with heel spur. One half of the patients underwent ESWT with an *Orthima* electrohydraulic shock wave source (Direx Systems Corporation) and the other half were sham-treated. The shock wave generator is mounted on a mobile arm and equipped with a sonographic imaging system (7.5 MHz probe). Symptoms were evaluated by means of the VAS. Changes in the dimension of the calcaneal spur were evaluated by X-rays and variations in the grade of *enthesitis* (inflammation at the region where tendons insert into the bone) were evaluated using ultrasound. A significant decrease of the VAS was observed in the ESWT group. Reduction of the *enthesophytosis* was recorded in 30 % of the ESWT patients. Significant changes in the grade of *enthesitis* were only observed after 1 month. In the sham-treated group, no significant decrease of the VAS, *enthesophytosis*, and *enthesitis* were observed. The main conclusion of the study was that ESWT is safe and improves the symptoms of most patients suffering from painful heel.

A study to investigate the clinical outcomes of ESWT on calcaneal spurs of 108 patients and their correlation with radiologic changes was reported by Yalcin et al. (2012). Each patient underwent radial pressure wave therapy once a week for 5 weeks (2000 pressure waves starting at an EFD of 0.05 mJ/mm^2 and increasing up to 0.4 mJ/mm^2) with a *DolorClast* (Electro Medical Systems). After therapy, approximately 67 % of the patients reported no pain; however, there was no correlation between clinical outcome and radiologic changes. The authors concluded that even without radiologic change, ESWT significantly reduces most patients' complaints about heel spurs.

To investigate the effect of shock waves on not pathologically altered bone, Gerdesmeyer and coworkers (2015b) treated 45 patients with a clinically relevant plantar heel spur as part of a standardized ESWT. The authors investigated whether focused shock waves (EFD = 0.32 mJ/mm^2) have an osteoinductive effect. To do so, the bone mineral density (BMD) and bone mineral content (BMC) of the treated calcaneus were determined. ESWT was performed with an *Epos Fluoro* electromagnetic shock wave source (Dornier MedTech GmbH). Each patient was treated twice with 2000 shock waves at a delivery rate of 2 Hz. The interval between sessions was 2 weeks. An increase in bone mineral density could be observed 6 weeks after the last session. The result was statistically significant 12 weeks after ESWT. Nevertheless, according to the authors, the optimum EFD and number of applied shock waves will have to be determined in further studies.

6.8 Achilles Tendinopathy

Achilles tendinopathy is a chronic condition that appears after a failed healing response in more than 5 % of the population. It is normally attributed to running and jumping activities; however, it also appears in sedentary persons. The most common symptoms are pain, swelling, and loss of function. Its management has been controversial. Several non-operative treatment modalities, such as eccentric loading exercises, heel lifts, anti-inflammatory drugs, massage, local glucocorticosteroid injections, low level laser therapy, and radiofrequency, are used. Surgery is recommended after failed conservative management of at least half a year.

Initial sonographic and histological results of the effects of shock waves on the Achilles tendons of rabbits were reported by Rompe et al. (1998b). Other authors exposed the tendon-bone junction of rabbits to 500 shock waves (EFD = 0.12 mJ/mm^2) and reported that treated tendons had significantly more neo-vessels and angiogenesis-related markers, and proliferating cell nuclear antigen than untreated tendons (Wang et al. 2003a). The same group found that shock waves promoted the formation of new vessels at the tendon-bone junction of the Achilles tendons in dogs (Wang et al. 2002a).

The use of pressure waves to treat patients suffering from Achilles tendinopathy has been reported as successful by several authors. Furia (2006 and 2008) obtained promising treatment outcomes using an EFD above 0.5 mJ/mm^2. After a 4-month follow-up of a randomized controlled trial, Rompe et al. (2007) concluded that eccentric loading and low-energy radial pressure waves showed comparable outcomes for the management of chronic recalcitrant tendinopathy of the main body of the Achilles tendon. Approximately 60 % of the patients had a significant improvement. In a third non-treated group (rest only) 20 % of the patients also showed improvement. In a following study, Rompe and colleagues (2008) demonstrated that in the management of chronic recalcitrant Achilles tendinopathy, eccentric loading applied to 25 patients was inferior to 2000 radial pressure waves (three sessions spaced 1 week apart, EFD 0.12 mJ/mm^2, pressure wave rate 8 Hz) produced by a

DolorClast (Electro Medical Systems) to the same number of patients. Kearney and Costa (2010) reviewed several publications to analyze the evidence for interventions specific to insertional Achilles tendinopathy. Their main finding was that there is a consensus that methods, such as eccentric loading and shock wave therapy, should be used before surgery.

A study to evaluate shock wave therapy using a *Piezoson 100* (Richard Wolf GmbH) at an EFD between 0.12 and 0.51 mJ/mm^2 for Achilles tendinopathy on 48 patients by Rasmussen et al. (2008) led to a clinically relevant effect with improvement of the American Orthopaedic Foot and Ankle Society (AOFAS) score. Each patient received four sessions of 2000 shock waves during 1 month (one session per week). Pain was reduced in both the sham and the ESWT group.

A long-term follow-up observational study to evaluate the effectiveness of ESWT in the symptomatic treatment of Achilles tendinopathies over time was published by Vulpiani and coworkers in 2009. The analysis included 127 tendons. Patients underwent ultrasonography, magnetic resonance imaging, and X-rays. A minimum of three and a maximum of four sessions of 1500–2500 electromagnetically generated focused shock waves (EFD between 0.08 and 0.40 mJ/mm^2) were administered using ultrasonic guidance at an interval from 2 to 7 days. Satisfactory treatment outcome was achieved in approximately 47 % of the tendons at a 2-month follow-up, 73 % of the tendons at medium-term follow-up (6–12 months), and 76 % of the tendons after 13–24 months. All treatments were done without anesthesia.

The results of three weekly radial pressure wave sessions to 60 patients with Achilles tendinopathy were described in an article published by Saxena et al. (2011). Each patient received three sessions of 2500 pressure waves generated with a Storz *D-Actor 200* (Storz Medical AG) at a frequency between 11 and 13 Hz (air compressor pressure 2.4 bar). No anesthesia was required. Overall, approximately 78 % of tendons improved by at least one year after radial pressure wave therapy. No adverse effects were observed, indicating that the therapy is a safe and effective option for the treatment of Achilles tendinopathy.

Al-Abbad and Simon (2013) reported a systematic review of four randomized controlled trials and two pre-post study designs on the effectiveness of ESWT in the treatment of insertional and non-insertional Achilles tendinopathies. Pain and foot/ankle or lower extremity function scores were the outcomes of interest. Treatment sessions ranged from three to five and the time interval between sessions was 1 week to 1 month. The number of pressure pulses applied per session varied between 1500 and 2000 and the EFD ranged between 0.08 and 0.51 mJ/mm^2. The analysis revealed that in four of the reviewed studies there was evidence of the effectiveness of ESWT in the management of patients with chronic Achilles tendinopathies (minimum follow-up time: 3 months). The authors also concluded that combining ESWT with eccentric loading showed superior results.

Comparison of reported shock wave and pressure wave therapy to patients suffering from Achilles tendinopathy should be made with care, because different shock wave sources and protocols may have been used. Furthermore, in many cases clinical results were evaluated with different criteria. Nevertheless, most specialists believe that ESWT should be considered together with other interventions for

Achilles tendinopathy. Results of randomized placebo-controlled trials have shown a high evidence of efficacy of ESWT in chronic Achilles tendinopathy (Gerdesmeyer et al. 2015a). As in most ESWT modalities, standardization of treatment protocols is still needed.

6.9 Tendinopathy of the Shoulder

The term *tendinopathy of the shoulder* includes both *calcific tendinitis of the shoulder* and *non-calcific tendinitis of the shoulder. Calcific tendinitis of the shoulder* or *calcified rotator cuff tendinitis* is a very common cause of shoulder pain, characterized by crystalline calcium phosphate deposition in the rotator cuff (shoulder) tendons causing pain, inflammation, and limitation of range of motion (Moya et al. 2015). Some possible causes are vascularization deficiencies and degenerative changes in tendinous tissue of the rotator cuff. Treatment options are anti-inflammatory drugs, percutaneous needle aspiration, injection with steroids, electrical stimulation, therapeutic ultrasound, and open or arthroscopic surgery.

The first reports of ESWT to treat patients suffering from shoulder tendinopathy were published more than 20 years ago (Rompe et al. 1995b). Since then, controversial results have been reported on the effectiveness of shock waves and radial pressure waves for patients suffering from tendinopathy of the shoulder. In general, the results are not favorable for the treatment of non-calcareous tendinopathy; however, several articles report successful treatment outcomes in cases of calcareous tendinopathy. So far there is no consensus on whether radial waves or focused shock waves are more efficient to treat tendinopathies of the shoulder. Compared with shock wave therapy, radial pressure pulses have the advantage that they are less painful and can be administered without anesthesia. Both shock waves and radial pressure pulses are targeted on the calcification by palpation, X-rays, or ultrasound. Figure 6.16 shows the case of a male patient (age 44 years) suffering from calcified tendinopathy of the shoulder, before and after shock wave treatment. The patient recovered the full range of motion and was symptomless 60 days after ESWT.

Successful treatment of tendinopathies of the shoulder using ESWT has been reported in several articles (Loew et al. 1995; Rompe et al. 1998a, 2001b; Spindler et al. 1998; Wang et al. 2001c; Daecke et al. 2002; Jakobeit et al. 2002; Cosentino et al. 2003; Pan et al. 2003; Harniman et al. 2004; Peters et al. 2004; Pleiner et al. 2004; Krasny et al. 2005; Cacchio et al. 2006; Albert et al. 2007; Mouzopoulos et al. 2007; Hsu et al. 2008; Vavken et al. 2009; Piontkowski et al. 2010; Huisstede et al. 2011; Lee et al. 2011; Ioppolo et al. 2013). According to some authors (Moya et al. 2015), the absence of a dense calcification rim around the rotator cuff is a good predictor of treatment outcome. Even if ESWT is considered a safe and effective procedure to treat calcific tendinitis in the shoulder, serious complications such as osteonecrosis of the humeral head after shock wave treatment have been reported (Durst et al. 2002; Liu et al. 2006).

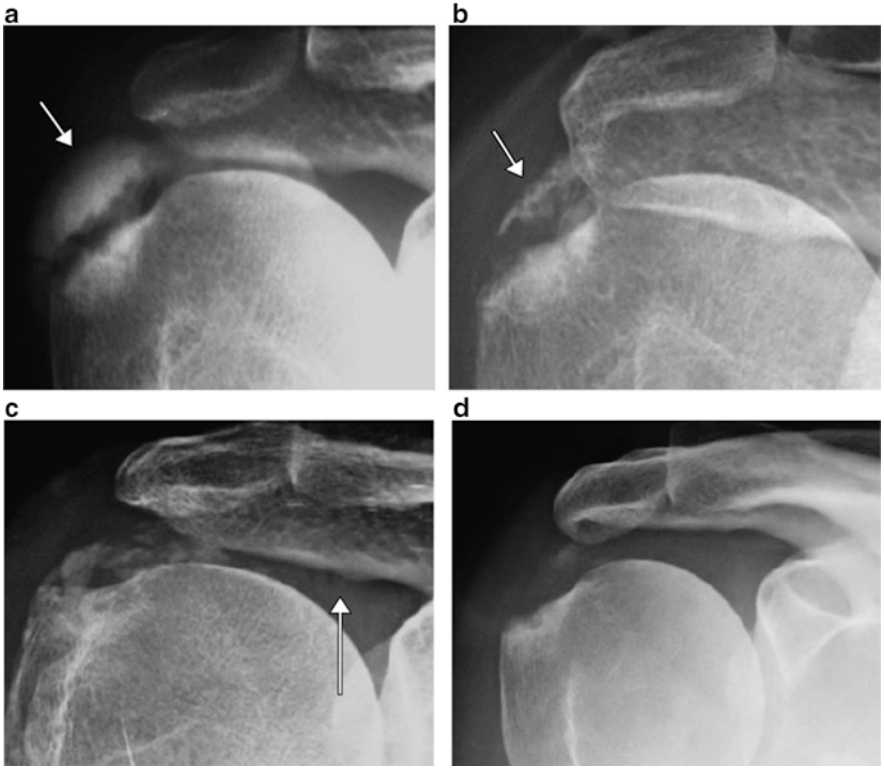


Fig. 6.16 X-ray images of a calcified tendinopathy of the shoulder (**a**) before ESWT, (**b**) and (**c**) 30 days after receiving a single session of 4000 shock waves (EFD = 0.35 mJ/mm^2) with a *Duolith SD1* electromagnetic shock wave source (Storz Medical AG, Tägerwilen, Switzerland) and (**d**) 60 days after therapy. The *arrow* in (**a**) shows the extension of the calcifications. Small portions of calcium salts migrating medially can be seen (*arrow*) in image (**c**). (Courtesy of L. Guiloff and M. Brañes)

Rompe and colleagues achieved complete or partial disintegration of the calcium deposits after ESWT in approximately 63 % of the cases (Rompe et al. 1997b). The same group published that at a 6-month follow-up, a 0.28 mJ/mm^2 EFD significantly increased the percentage of calcification disappearance in the shoulder, compared to an EFD of only 0.06 mJ/mm^2 (Rompe et al. 1998a). In both groups 1500 shock waves were administered with an electromagnetic shock wave source manufactured by Siemens Healthcare GmbH, Erlangen, Germany. A few years later, they reported a randomized clinical trial to evaluate shock waves to treat calcareous tendinopathy of the rotator cuff (Rompe et al. 2001b). Comparing ESWT with conventional surgery revealed that after 1 year of follow-up, the calcification was eliminated in 47 % of the shock wave-treated patients and in 85 % of the surgical group.

Wang et al. (2003c) reported the results of a two- to three-year follow-up of ESWT to 39 shoulders with calcific tendonitis. About 61 % of the patients were

complaint free, 30 % reported to feel significantly better, and 3 % felt slightly better. No changes were reported in approximately 6 % of the treated patients. In the control group (6 shoulders) approximately 17 % reported a slight improvement, while the rest did not feel any changes. A prospective, randomized controlled trial on two groups of patients suffering from calcific tendonitis was reported by Krasny et al. (2005). Half of the patients were treated with ultrasound-guided needling followed by ESWT. The remaining patients were treated only with ESWT. Shock wave therapy consisted of a single session of 200 shock waves at low-energy level, followed by 2500 shock waves at an EFD of 0.36 mJ/mm^2, generated with an electromagnetic *Epos Fluoro* (Dornier MedTech GmbH) unit. All patients had a significant improvement; however, better outcome was obtained in the first group (needling followed by ESWT). No severe side effects were observed.

In 2006 a single-blind, randomized study to analyze the success of radial pressure wave therapy on restoration of the shoulder function, pain relief, and resolution of calcific tendinitis using a *Physio Shock Wave Therapy* device (Elettronica Pagani, Paderno Dugnano, Italy) with a 15-mm-head applicator was reported (Cacchio et al. 2006). Patients in the treatment group received 4 sessions, each consisting of 500 pulses generated at an air compressor pressure of 1.5 bar and a frequency of 4.5 Hz, followed by 2000 pulses produced with an air pressure of 2.5 bar and a frequency of 10 Hz. The control group received low-dose rESWT: four sessions consisting of five impulses with a pressure of 1.5 bar and a frequency of 4.5 Hz and 20 impulses with a pressure of 2.5 bar and a frequency of 10 Hz. The authors concluded that rESWT is effective in improving shoulder function, reducing pain and eliminating calcifications. VAS results were comparable to scores published for extracorporeal shock wave therapy by Gerdesmeyer et al. (2003). Furthermore, the shoulder function (evaluated with the UCLA shoulder rating scale) was comparable to previously published results with ESWT. Their results obtained with radial pressure pulses were superior in dissolving calcifications, compared to the study by Rompe et al. (2001b). Nevertheless, more research is still required to evaluate if, and under which circumstances, it is more advisable to use extracorporeal radial pressure waves instead of shock waves. Societies, such as the ISMST and the DIGEST, i.e., the German International Society for ESWT ("Deutschsprachige Internationale Gesellschaft für Extrakorporale Stosswellentherapie"), do not consider studies including placebo groups that also received pressure pulse treatment.

Albert et al. (2007) compared high-energy ESWT (EFD between 0.28 and 0.60 mJ/mm^2) with low-energy therapy (EFD less than 0.08 mJ/mm^2) to treat calcific tendinitis of the shoulder. A total of 40 patients were assigned to each group and treated with a Modulth SLK electromagnetic shock wave source with fluoroscopic and sonographic imaging (Storz Medical AG). After a follow-up time of almost 4 months post-treatment, a statistically significant improvement was reported only in the high-energy group. Saithna et al. (2009) reviewed the effect of high-energy shock waves in treating calcific tendinitis of the rotator cuff, concluding that 6 months after treatment there was evidence on the effectiveness of the treatment in improving the Constant–Murley scores compared to a placebo group. A comparison between the effects of applying 6000 shock waves with a *Minilith*

SL1 unit (Storz Medical AG) in three sessions at an EFD of 0.78 mJ/mm^2 and the same number of waves at an EFD of 0.33 mJ/mm^2, to treat patients with a rotator cuff tendinopathy without calcification was reported by Schofer and colleagues in 2009. The statistical analyses revealed that there was no significant difference between the high- and low-energy group after 12 weeks and 1-year follow-up. A meta-analysis performed by Vavken et al. (2009) revealed that ESWT is an effective, dose-dependent therapy for calcific tendinitis. A review of randomized controlled studies to evaluate the midterm effectiveness of ESWT for calcified rotator cuff tendinitis showed evidence of pain reduction and improvement of shoulder function; however, no quantitative analysis could be made because different outcome measures were used in the included trials (Lee et al. 2011).

In a thorough review of 11 shock wave treatments of calcareous tendinopathy and six of tendinopathy without calcification, Huisstede et al. (2011) concluded that only high-energy shock waves (EFD above 0.28 mJ/mm^2) were effective for treating calcific rotator cuff tendinosis. Furthermore, there was no evidence for the effectiveness of shock waves to treat non-calcific rotator cuff tendinosis. Engebretsen et al. (2011) compared the results of radial pressure wave therapy with the treatment by means of supervised exercises to patients suffering from subacromial shoulder pain. The study included 104 patients with pain lasting 3 months or more. Half of the patients received rESWT (one session per week for 4–6 weeks) and the remaining patients were treated with two weekly exercise sessions during 12 weeks. No placebo control group was included. In the rESWT and exercise group, 52 % and 60 % of the patients were categorized as clinically improved, respectively. The main conclusion of this study was that after a one-year follow-up, no significant difference was found between both treatment modalities. A randomized controlled trial (RCT) published by Liu et al. (2012b) revealed that shock wave-treated patients suffering from tendinopathy of the long head of the biceps showed significantly better results than patients belonging to the placebo group.

The assumption that shock waves stimulate rotator cuff healing after arthroscopic repair was studied by Kim et al. (2012) on 71 patients. One group of patients underwent ESWT 6 weeks after surgery, while a second group did not receive shock wave treatment. Six months after surgery the cuff integrity was assessed with computed tomographic arthrography. Even if there were no complications associated with the shock wave treatments, the authors could not prove that ESWT stimulates rotator cuff healing after arthroscopic rotator cuff repair.

The results of a study performed to investigate the efficacy of ESWT for non-calcifying supraspinatus tendinopathy (NCST) of the rotator cuff were published by Galasso et al. (2012). Two sessions of 3000 shock waves (EFD = 0.068 mJ/mm^2), spaced by 7 days, were administered with a *Modulith SLK* shock wave source (Storz Medical AG) using an in-line 7.5 MHz ultrasound transducer to focus the shock waves at a region 10 mm proximal to the insertion of the tendon in the bone. Treatment outcomes of the ESWT group and the patients in the placebo group were evaluated using a clinical method of functional assessment of the shoulder. Significantly higher scores for pain and range of motion (ROM) were observed in the ESWT group, revealing that patients suffering from NCST may benefit from

shock wave treatment. Nevertheless, this therapy option is still controversial. Efe et al. (2014) analyzed the efficacy of ESWT in patients treated for NCST by revisiting patients ten years after their first consultation. All patients had received three sessions of 6000 impulses (EFD = 0.11 mJ/mm^2) between 1999 and 2000. No significant changes could be found between the ESWT group and the placebo group that received 6000 impulses of a sham ESWT in the same period.

Brañes et al. (2012) studied the responses of human rotator cuff tissue to the application of ESWT. Each patient received a single session of 4000 shock waves (EFD = 0.3 mJ/mm^2) to the affected shoulder under ultrasound guidance using an *Orthospec* (Medispec Ltd., Yehud, Israel) or a *Duolith* (Storz Medical AG) shock wave generator. Tendon tissue biopsies were evaluated after treatment. The authors concluded that focused shock wave treatment is associated with an increased neovascularization and neolymphangiogenesis in rotator cuff tendinopathy. An immunohistochemical evaluation revealed enhancement in the healing response in shock wave-treated tendons. In another study, Bannuru et al. (2014) compared high-energy versus low-energy ESWT or placebo as a therapy for calcific and non-calcific tendinitis of the shoulder. Their study reveals that high-energy treatments were significantly better than placebo in improving function, resorption of calcifications, and decreasing pain in the treatment of calcific tendinitis; however, no significant differences were detected between the placebo groups and ESWT groups for the treatment on non-calcific tendinitis. According to the authors, high-energy ESWT may be underutilized for the treatment on calcific tendinitis and could be a good alternative to surgical interventions. Pain evaluation was done predominantly by a visual scale pain score, which goes from 0 or 1 (no pain) to 10 (maximum pain). The shoulder function was evaluated according to well-known standardized tools (Constant and Murley 1987) as well as the shoulder pain and disability index and the UCLA shoulder rating scale. The resolution of calcifications was done radiographically and sonographically. Petechiae, small bruises and hematomas, erythema, and pain were the most frequently reported adverse effects; however, none of them was serious.

A representative prospective randomized placebo-controlled multicenter trial of radial pressure wave therapy in patients with chronic non-calcifying or calcifying tendinitis of the rotator cuff was published by Kolk and coworkers (2013). Patients were randomly assigned to one of two groups. The first group ($n = 44$) received three radial pressure wave sessions consisting of 2000 pulses delivered at a rate of 8 Hz (EFD = 0.11 mJ/mm^2) at an interval of 10–14 days, using a *DolorClast* (Electro Medical Systems). The second group ($n = 38$) received placebo treatment with an identical looking probe that emitted the same sounds as the radial pressure wave device. Results showed that the VAS score, a Constant–Murley score (CMS) (Constant and Murley 1987), and a simple shoulder test (SST) (van Kampen et al. 2012) score significantly improved in both groups at 6 months after radial pressure wave or sham treatment. At 6 months, no significant difference between the two groups was observed in any of the scores. According to this study, rESWT with the device and at the dose mentioned above does not reduce pain or improve function in either non-calcifying or calcifying tendinitis compared with placebo treatment.

The reports of positive outcomes in the treatment of rotator cuff calcifications expanded the use of ESWT to other shoulder pathologies. A thorough review of the state of indications and evidence-based practice was published by Moya and collaborators. According to the present experience of ESWT outcomes for shoulder pathology, one to three sessions of 2000 focused shock waves at an EFD between 0.19 and 0.32 mJ/mm^2 are recommended when using an electrohydraulic shock wave source, and two to three sessions of 2000 shock waves at an EFD of 0.35 mJ/mm^2 with electromagnetic shock wave devices (Moya et al. 2015). In the case of rESWT, the authors suggest up to five therapy sessions of 4000 radial pressure waves, applied at intervals between 1 and 2 weeks, without local anesthesia. Depending on the ballistic pressure wave device, the air compressor pressure should be adjusted between 4 and 5 bar.

6.10 Epicondylitis of the Elbow

Lateral epicondylitis (LE) is the most common form of tendinitis of the elbow. It should be named *lateral epicondylosis*, because it is a degenerative change in the tendons that go from the arm muscles to the elbow and not an inflammation (Kraushaar and Nirschl 1999; Nirschl and Ashman 2004). It is also commonly known as *tennis elbow*; however, it may be a consequence of many other activities that implicate repetitive extension of the wrist. Pain in the outer part of the elbow results from overuse or injury of the tendons. Rest, activity modification, anti-inflammatory medications, and physical therapy are conservative measures. Corticosteroid injections and orthotic devices are also used. Some patients with LE require open surgery or laparoscopic procedures to remove degenerative tissue and repair abnormalities.

Rompe and colleagues reported the first ESWT results on patients suffering from tennis elbow (Rompe et al. 1995a). Three treatments (1000 shock waves each, EFD ~ 0.06 mJ/mm^2) were successful in about 90 % of patients. One year later, the same group reported about the analgesic effect of shock waves on chronic tennis elbows. At the final review (24 weeks after treatment), excellent results were obtained in almost 50 %, and acceptable results in approximately 40 % of patients with chronic tennis elbow after a few sessions of several hundreds of shock waves. Shock waves were generated with an *Osteostar* (Siemens Healthcare GmbH) experimental device, in which an electromagnetic shock wave source was integrated into a mobile fluoroscopy unit. The C-arm was centered on the lateral epicondyle and the shock waves coupled to the elbow towards a water-filled cushion and a flexible membrane (Rompe et al. 1996). Since then, many articles reported success of ESWT in patients with LE of the elbow (Wang and Chen 2002; Rompe et al. 2004; Furia 2005; Spacca et al. 2005; Radwan et al. 2008; Ozturan et al. 2010; Piontkowski et al. 2010). The FDA approved ESWT for epicondylitis in 2003.

While some studies report favorable effects of ESWT in the treatment of LE (Rompe et al. 1996; Stasinopoulos and Johnson 2005), other authors could not find

a meaningful difference between ESWT and the control groups (Chung and Wiley 2004; Ho 2007; Buchbinder et al. 2009). A double-blind, randomized controlled trial on approximately 70 patients to determine whether ultrasound-guided ESWT reduced pain and improved function in patients with tennis elbow was reported by Staples et al. (2008). Little evidence was found to recommend ESWT for the treatment of LE. Haake et al. (2002b) published a thorough review concluding that they could not detect a significant efficacy of ESWT for lateral elbow pain, and a double-blind randomized trial performed by Speed and colleagues (2002) concluded that there is no benefit of ESWT compared to sham treatment in patients with LE. As in other shock wave treatment modalities mentioned in this chapter, the reported differences in regard to the management of LE can be attributed to different clinical protocols, therapy devices, patient selection, and a different methodology to evaluate treatment outcomes.

After a systematic and qualitative analysis of 10 RCTs, Rompe and Maffulli (2007) could not find a consensus with regard to differentiation between low-energy and high-energy shock waves for ESWT of lateral elbow tendinopathy. To determine the safety and effectiveness of ESWT to treat patients suffering from LE of the elbow, Buchbinder et al. (2009) reviewed nine placebo-controlled studies including more than a thousand patients. Most of the studies found no significant differences between the ESWT group and the placebo group. The authors concluded that there is evidence that ESWT offers little or no benefit in comparison with placebo. More recently Dingemanse et al. (2014) reported findings similar to those of Buchbinder and colleagues, and Kertzman et al. (2015) concluded that the reviews included in their study present results that are inconsistent with the use of ESWT to treat patients suffering from LE.

The therapeutic effects of ultrasound therapy, hot pack, massage, local corticosteroid injection, and 10 sessions of ESWT were compared clinically and ultrasonographically by Gündüz et al. (2012) in 59 patients with LE. Pain was evaluated with the VAS. Dynamometers were helpful to evaluate grip and pinch strength before treatment and at different periods of time after treatment. Patients were also evaluated with ultrasonography before and 6 months after treatment. The pain scores decreased significantly in all patients on the first, third, and sixth month of treatment. The pinch strength and the ultrasonographical findings did not change in any group at any time evaluated. Corticosteroid injection and ESWT had a positive effect on pain and grip strength in the early period of the treatment; however, the increase in grip strength lasted longer in patients that received ESWT.

Lee and colleagues (2012) evaluated the effectiveness of radial pressure waves for patients suffering from lateral or medial epicondylitis, compared to local steroid injection. Their study included patients newly confirmed as lateral or medial epicondylitis. Patients in the pressure pulse-group ($n=12$) received one session per week (2000 pressure pulses, EFD between 0.06 and 0.12 mJ/mm^2) using a *DolarClast* device (Electro Medical Systems) during 3 weeks, while the second group ($n=10$) was treated once with a solution of 10 mg of triamcinolone mixed with 1 % lidocaine. Evaluation was performed using the Nirschl score (Nirschl 1992), the 100 point scoring system (Jung et al. 2009), and the Roles and Maudsley

scores (Roles and Maudsley 1972). The results showed that the pressure wave-treated patients improved as much as the patients that received steroid injection. The main conclusion of this study was that radial pressure waves can be a treatment option in patients for whom steroid injection is problematic. These conclusions should not be generalized to all ESWT treatment modalities, because they may depend on the clinical devices and treatment protocols used.

Thiele et al. (2015a) reported a thorough analysis of several studies which were performed following the guidelines of the ISMST and the DIGEST and concluded that the evidence supports the use of ESWT for lateral epicondylitis with symptoms beyond 3 months. The authors also commented that ESWT should only be used without local anesthesia. In the cases of chronic indications, the follow-up time ideally should be one year. Comparison of treatment protocols and outcomes is difficult as there is a high diversity of methodologies, scores, and end-points. It only has sense to compare devices that operate using the same physical principle. Figure 2.15 shows a typical therapy on the lateral *epicondyle* with a radial pressure wave device.

6.11 Patellar Tendinopathy

Patellar tendinopathy, sometimes also referred to as *patellar tendinitis* or *jumper's knee*, appears because of a repetitive overloading of the extensor mechanism of the knee, exceeding the natural healing mechanism. It causes pain in the front part of the knee, begins as an inflammation of the patellar tendon and is a common cause of pain in athletes that do explosive jumping movements. Treatment outcome in most patients with patellar tendinopathy is good in the early stages. Few patients require a surgical intervention, in which the damaged tissue from the tendon is removed and the blood flow is stimulated to promote healing. According to several published studies, it seems that ESWT is effective in the management of patients with patellar tendinopathy resistant to conservative treatments (Peers et al. 2003; Vulpiani et al. 2007; Wang et al. 2007; van Leeuwen et al. 2009; Piontkowski et al. 2010; Zwerver et al. 2010). Reports of patients that received three to five sessions of 2000 shock waves each (EFD = 0.17 mJ/mm^2), generated with an electromagnetic source, concluded that although ESWT appears to be a useful adjunct in the treatment of chronic patellar tendinopathy, further research is needed to determine the mechanism of pain relief, the appropriate follow-up time, and the most efficient EFD and number of shock waves (Taunton et al. 2003).

A study by Wang et al. (2007) compared 30 shock wave-treated knees with 24 knees that received a conservative therapy. Patients in the first group were treated with 1500 shock waves (EFD = 0.18 mJ/mm^2) generated with an *OssaTron* shock wave source (High Medical Technologies, AG) as the one shown in Fig. 2.14. A two- to three-year follow-up revealed 43 % excellent, 47 % good, and 10 % fair outcomes in ESWT patients. No poor treatment outcome was reported in the ESWT group. None excellent, 50 % good, 25 % fair, and 25 % poor outcomes were obtained for patients treated with conservative methods. A few years later, Zwerver et al. (2011)

published the results of a randomized controlled clinical trial designed to evaluate the effectiveness of shock wave treatment on athletes with mild symptoms of patellar tendinopathy playing volleyball, basketball, or handball. A group of 31 athletes was treated with three sessions of 2000 shock waves generated at a rate of 4 Hz with a *PiezoWave* ESWT device (Richard Wolf GmbH) at 1-week intervals, whereas another same-sized group received a placebo treatment. Shock wave therapy was started at low EFD (0.1 mJ/mm^2) and increased after every 100 shock waves, as far as tolerated by the patient (up to a maximum of 0.58 mJ/mm^2). Shock wave coupling was achieved using pads with a focus of 5 or 10 mm. The conclusion of the study was that ESWT has no benefit over placebo treatment in the management of actively competing jumping athletes with early symptomatic patellar tendinopathy.

To assess whether single ESWT is effective for the management of chronic patellar tendinopathy, Furia et al. (2013) treated 33 patients with low-energy shock waves, while a second group of the same size was treated with other forms of non-operative therapy. The evaluation was done by analyzing the scores of well-known assessment scales. After one year, the percentage of patients with successful results was significantly greater in the shock wave-treated group. Because of this, the authors concluded that a single ESWT session is an effective treatment for chronic patellar tendinopathy.

The effectiveness of injections of platelet-rich plasma for athletes suffering from chronic patellar tendinopathy was compared with ESWT by Vetrano and colleagues in a randomized controlled single-center trial, with 12 months of follow-up (Vetrano et al. 2013). Patients in the first group ($n=23$) received two injections separated by 1 week at the affected tendon portion. The second group of athletes ($n=23$) received three treatments of 2400 focused shock waves (EFD 0.17–0.25 mJ/mm^2) separated by 48–72 h using a *Modulith SLK* shock wave generator (Storz Medical AG). At 2, 6, and 12 months after treatment, the patients completed a questionnaire, which evaluated the severity of symptoms, function, and ability to participate in sport. A VAS was used to assess pain. The conclusions of the study were that both therapy modalities are safe and effective in the treatment of chronic patellar tendinopathy. According to the authors, comparable results were achieved in both groups at short-term, with better results in the first group after 6 and 12 months.

6.12 Bone Healing

A *delayed union* is defined as a fracture that does not heal completely within 4 months and if healing does not occur after 6 months it is called *pseudarthrosis*. Delayed bone unions and pseudoarthrosis generally affect adults. Approximately 2–7 % of all fractures evolve into pseudoarthrosis (Rodriguez-Merchan and Forriol 2004).

The idea to focus shock waves on bone fractures appeared during in vivo experiments to study the effects of shock waves on living tissue. A crucial observation was an osteogenic response after shock waves striking the pelvis (Graff et al. 1989).

Studies published by Graff and coworkers (Graff et al. 1988a) stimulated the use of shock waves in orthopedics and many reports of in vivo effects of shock waves followed (Yeaman et al. 1989). A benefic effect of shock waves on fracture healing in rats was reported by Haupt et al. (1992), and the effectiveness of shock waves to treat hypertrophic non-unions in dogs was published two years later by Johannes et al. (1994).

Among the first to perform treatments of delayed and non-union of fractures with shock waves were Valchanou and Michailov (1991), Bürger et al. (1991), and Schleberger and Senge (1992). Application of several hundred shock waves induced bony union in about 40–85 % of the patients. The hypothesis was that micro-trauma produced by the shock waves lead to revascularization and triggered the healing process (Haupt 1997; Rompe et al. 1997a, 2001a; Vogel et al. 1997; Beutler et al. 1999; Schaden et al. 2001; Wang et al. 2001a). Enhanced callus formation and induced cortical bone formation was demonstrated by Wang et al. (2001b) on acute fractures of the tibia in a dog model. Moreover, in vivo experiments with rabbits revealed that the effect of ESWT on bone mass and strength seemed to be dose dependent (Wang et al. 2004b). As mentioned before, today there is a consensus that the main therapeutic mechanism of focused shock waves in cases of pseudarthrosis is mechanotransduction. Several authors demonstrated that ESWT stimulates osteoblasts and periosteal cells, osteogenic differentiation, and the expression of growth factors (Rompe et al. 2001a; Schaden et al. 2001; Wang et al. 2002b, 2004a; Martini et al. 2005; Moosavi-Nejad et al. 2006; Amelio and d'Agostino 2014). The upregulation of genes involved in skeletal development and osteoblastic lineage differentiation seems to be affected by the osteoblast proliferation induced by the shock waves (Hofmann et al. 2008). It is believed that the effect of shock waves on the transduction signal in the bone cells occurs by activation of the cyclin E2/CDK2 complex (proteins that control the progression of cells by activating enzymes that are critical in metabolism, protein regulation, cellular transport, and other cellular pathways) as well as extracellular signal-regulated kinase (ERK) and p38 kinase activity (Chen et al. 2004; Tamma et al. 2009). Shock waves have a favorable effect on the colonization of bioscaffolds (Muzio et al. 2010). After ESWT, osteoblast-like cells proliferate and increase the expression of alkaline phosphatase (ALP), osteocalcin, and collagen type I. Nitric oxide (NO) is involved in bone metabolism. It is believed that there is a correlation between shock wave action and an increase in the production of NO, as well as of prostaglandin E2 (PGE-2) and prostaglandin I2 (PGI-2) in osteocytes (Muzio et al. 2010). Clinical investigations seem to confirm this (Wang et al. 2009e). PGE-2 stimulates osteoblasts to produce substances that enhance bone resorption by osteoclasts, and PGI-2 is a vasodilator and inhibits platelet activation.

If local mechanical stability is guaranteed, nowadays shock wave therapy is considered as a safe noninvasive alternative to surgery. Between 2500 and 5000 shock waves with an EFD between 0.4 and 0.6 mJ/mm^2 are recommended. Energy flux densities of up to 1.0 mJ/mm^2 may be used in cases of non-unions. Two sessions for short bones and up to five sessions for long bones, with intervals of 3 days or more,

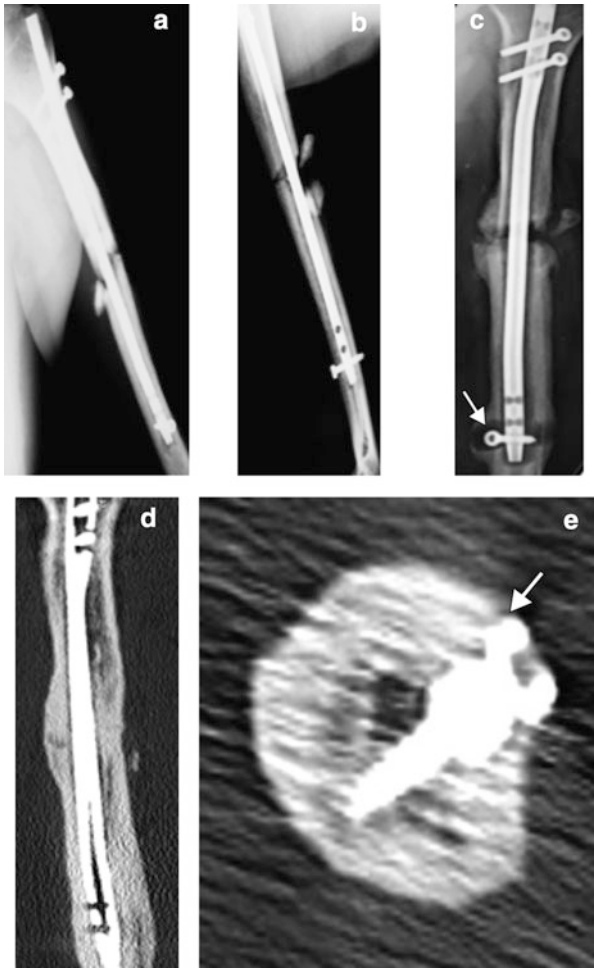


Fig. 6.17 X-ray images (**a**) and (**b**) show an open reduction internal fixation after trauma. (**c**) demonstrates non-healing and shows a loose screw (*white arrow*), and (**d**) is a CT-scan after ESWT, confirming complete bone healing. The ESWT consisted of three sessions of 6000 shock waves (EFD = 0.35 mJ/mm^2) with a *Duolith SD1* electromagnetic shock wave source (Storz Medical AG, Tägerwilen, Switzerland) from anterior and the same dose from lateral, adding 2000 shock waves (same EFD) to the region of a loose distal screw. Image (**e**) shows shock wave-induced bone reaction allowing re-attachment of the screw (*white arrow*). (Courtesy of L. Guiloff and M. Brañes)

are suggested (Amelio and d'Agostino 2014). A typical case of non-union after fracture before and after ESWT is shown in Fig. 6.17. Not only complete bone healing was achieved, but also re-attachment of a loose screw. As a second example, Fig. 6.18 shows images of a 36-year-old male patient after femur shaft fracture and atrophic non-union before and after shock wave therapy.

At a very high EFD, shock waves could produce complete fractures. This was demonstrated in vitro by Kaulesar Sukul et al. (1993) using rabbit femurs and tibiae. At in vivo experiments with lower energies it was found that shock waves enhance the healing of diaphyseal osteotomy in rabbits by achieving superior maximal torsion strength, but do not influence bone mineral density (BMD) values (Hsu et al. 2003). However, Saisu et al. (2004) observed an overgrowth and local increase in bone mineral content (BMC) in immature rabbit bones exposed to 1000 and 5000 shock waves (p^+ ~100 MPa). The release of substance P and prostaglandin E_2 after

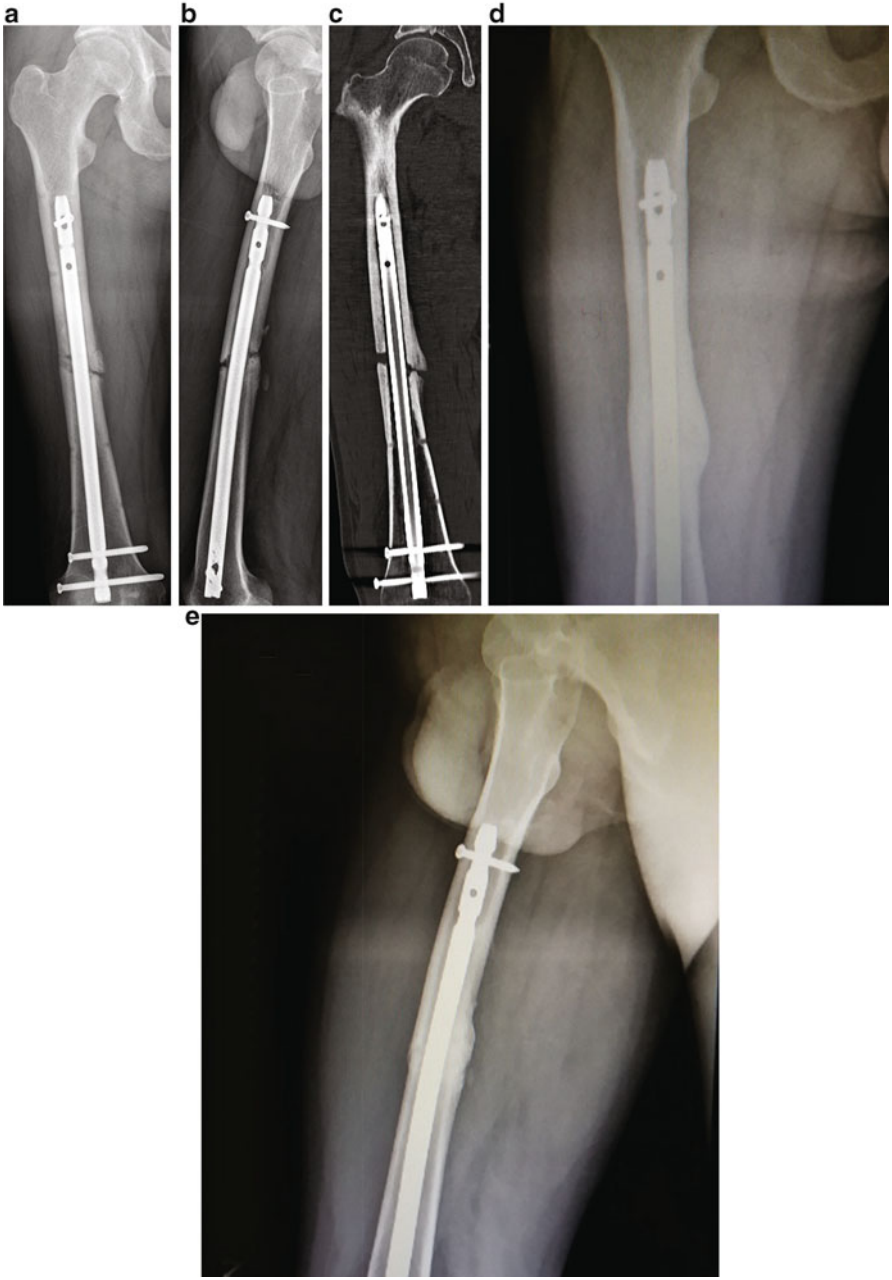


Fig. 6.18 Radiographic images of a femur shaft fracture and atrophic non-union, demonstrated in both X-ray planes (**a**) and (**b**) and coronal CT-scan (**c**). ESWT comprised three sessions (one per month) of 10,000 pressure pulses (EFD = 0.55 mJ/mm^2) applied with a *Duolith SD1* (Storz Medical AG, Tägerwilen, Switzerland), distributed almost circumferentially along bone rim fractures (protecting the position of posterior great vessels). Radiographic images (**d**) and (**e**) reveal complete consolidation 10 months after ESWT. (Courtesy of L. Guiloff and M. Brañes)

shock wave application to rabbit and rat models were demonstrated by Maier et al. (2003) and Wang et al. (2003b). Ikeda et al. (1999) observed shock wave-induced subperiosteal callus formation by creating small fractures on the cortex of a canine model. Tischer et al. (2008) studied the effects of shock wave application on bone. A dose-dependent increase of shock wave-induced periosteal bone formation was observed on the intact femur of rabbits. In this model, a minimum EFD of 0.5 mJ/mm^2 was required to induce the effect. The amount of new bone formation increased as the EFD was raised from 0.9 to 1.2 mJ/mm^2. Ozturk et al. (2008) evaluated the histology of immature rabbit epiphysis (rounded end of a long bone) exposed to underwater shock waves and concluded that ESWT stimulated epiphyseal growth and improved the epiphyseal plaque thickness. According to an in vivo study published by Dias Dos Santos et al. (2015), extracorporeal shock waves stimulate the regeneration and bone healing by increasing the concentration and prolonging the anabolism period of sulfated glycosaminoglycans in addition to early enhanced expression of hyaluronic acid.

Some groups have been using a single session of focused shock wave therapy as the first-line treatment for non-unions since 1998. According to the reports by Schaden and colleagues (Schaden et al. 2001, 2015) more or less 75 % of the referred patients suffering from a non-union fracture are suitable for ESWT. Consolidation of non-unions with ESWT can be achieved even in patients with multiple revision surgeries (Gerdesmeyer et al. 2015b). So far, the detailed biological mechanisms of ESWT in bone healing are not known. More studies, including proteomics and sequencing technologies, may help to reveal the phenomena involved (Cheng and Wang 2015).

ESWT was compared with surgical treatment in almost 130 patients with long-bone hypertrophic non-unions by Cacchio and colleagues (2009). Healing at 6, 12, and 24 months was equal in both groups, demonstrating that ESWT is as effective as surgery in stimulating the union of long-bone non-unions. A thorough review on results of ESWT to treat delayed unions/non-unions and fractures, published by Zelle et al. (2010) shows that the union rate in patients with delayed union/non-union fluctuated from 41 to 85 %. Their analysis included more than 900 patients who underwent up to three ESWT sessions. Their main conclusion was that ESWT is a promising treatment modality for fractures and delayed unions/non-unions; however, more studies are needed to further validate the technique. Elster et al. (2010) published a study with almost 200 patients treated with ESWT for tibia non-union determined at least 6 months after either operative or non-operative treatment. Therapy was performed under general or regional anesthesia with an *OssaTron* (Fig. 2.14) shock wave source (High Medical Technologies, Lengwil, Switzerland). Shock waves were focused at the fracture site using fluoroscopy. The total number of shock waves was equally divided along the proximal and distal margins of the non-union. The median number of shock waves administered was 4000 (EFD ~0.4 mJ/mm^2). Complete fracture healing at the time of last follow-up was diagnosed for approximately 80 % of the patients.

The number of fractures which healed at 3 and 6 months follow-up in patients suffering from non-unions on the base of the fifth metatarsal bone, treated either

with focused shock waves ($n = 23$) or surgery ($n = 20$) was compared retrospectively by Furia and coworkers (2010a). The ESWT group received between 2000 and 4000 shock waves (EFD = 0.35 mJ/mm^2) in a single session. Patients in the surgical group were treated with closed reduction and intramedullary screw fixation. Osseous healing at 3 months after treatment was achieved in 20 shock wave-treated patients and in 18 patients of the surgery group. One non-union of the ESWT group was consolidated 6 months after therapy. Only one post-ESWT petechiae was observed, whereas 11 complications were registered in the surgery group.

Focused shock wave therapy in patients suffering from non-unions of the carpal scaphoid was compared with surgery by Notarnicola et al. (2010). Their retrospective analysis included 58 patients in the ESWT group and 60 patients that underwent surgery. ESWT patients received three sessions (at a 72 h interval) of 4000 shock waves (mean EFD = 0.09 mJ/mm^2) with a *Minilith* (Storz Medical AG). Post-ESWT and post-surgery immobilization were identical. Analysis of the treatment outcomes revealed that at a 12-month follow-up period bony consolidation did not differ between both groups.

The effectiveness of ESWT to treat patients suffering from atrophic non-union of isthmic femoral shaft fractures, that were initially treated surgically using closed reamed nailing procedure, was reviewed by Kuo et al. (2015). ESWT was performed using an *OssaTron* shock wave source (Sanuwave Health, Inc., Alpharetta, Georgia, USA). Shock waves were applied in two planes at 45 and 60° relatively to the longitudinal axis of the femur. Each plane received 3000 shock waves generated at a voltage of 28 kV (EFD = 0.58 mJ/mm^2). Radiographs were obtained before ESWT and once a month after therapy for 1 year. Approximately 63.6 % of the cases achieved bony union after 6–13 months. Patients, who did not achieve bony union, received subsequent treatment with bone grafting with augmentative plating surgery and all achieved bony union within 5 months, demonstrating that ESWT does not negatively influence previous surgeries.

ESWT has also been successfully used in the treatment of stress fractures (Furia et al. 2010b). Stress fractures are common in athletes and result after excessive repetitive loads on the bone, causing an imbalance between the activity of the osteoclasts in bone resorption and the osteoblasts in bone formation. When these fractures fail to heal, surgical procedures are commonly used to stabilize the area, avoiding a complete fracture. After the first report of a stress fracture treated with shock waves in 1999 (Hotzinger et al. 1999), other authors published results of successful clinical outcomes (Gordon and Lynagh 2002; Leal et al. 2002; Leal 2006). For instance, single sessions of 2000–4000 shock waves at an EFD between 0.29 and 0.40 mJ/mm^2 generated by an *OssaTron* (Sanuwave Health, Inc.) electrohydraulic shock wave source significantly reduced the recovery times in athletes with stress fractures that did not respond to conventional treatments (Taki et al. 2007). Three to four sessions of 4000 shock waves at lower energy densities (between 0.09 and 0.17 mJ/mm^2) have been used to successfully treat athletes with stress fractures of tibias or metatarsals (Moretti et al. 2009a). According to a review by Leal et al. (2015), ESWT is a safe noninvasive therapy with a high rate of efficacy to treat stress fractures. The best results have been obtained using one or two

sessions of minimum 2000 focused shock waves with an EFD of approximately 0.2 mJ/mm^2.

A detailed review on the current status of ESWT for treating disorders in bone was published by Cheng and Wang (2015). Several factors, such as the time between trauma and ESWT, the site and type of fracture, as well as the immobilization of the lesion, influence the healing rate of bone non-unions (Cacchio et al. 2009; Elster et al. 2010; Furia et al. 2010a; Alvarez et al. 2011; Stojadinovic et al. 2011). Another review by Schaden and coworkers (2015) concluded that the treatment of fracture non-unions with electrohydraulic and electromagnetic shock wave sources is effective. The analysis also revealed that electrohydraulic shock wave generators have been used in a single session, whereas between two to four sessions are recommended for electromagnetic shock wave sources. It was possible to identify non-union gaps larger than 5 mm in long bones as a negative predictor for therapy outcome. The main conclusion of the review was that, since ESWT has been proven to be as effective as surgery, it should be considered as the first choice for the treatment of suitable non-union fractures.

6.13 Bone Vascular Diseases

Osteonecrosis of the femoral head, also called *avascular necrosis of the femoral head* (AVNFH), is a severe bone vascular disease with unknown etiology and an incidence of 0.1 %, involving all ages (Russo 2014). It is characterized by reduced local blood flow and death of the osteocytes and the bone marrow, associated with pain and loss of joint function. Conservative therapies have not been very successful and in its final stages the only possible treatment is prosthetic replacement.

In the initial stages of femoral head osteonecrosis, ESWT has been useful to reduce the size of the necrotic area (Wang et al. 2015a). It also may delay the need for total hip arthroplasty and reduce bone marrow edema patterns (Wang et al. 2005, 2008b). Positive outcomes of ESWT for the treatment of avascular necrosis of the femoral head have been published by several authors (Ludwig et al. 2001; Wang et al. 2005, 2015a; Russo 2014). Lin et al. (2006) and Wang et al. (2009b) reported ESWT for osteonecrosis of the femoral head in systemic lupus erythematosus and for hip necrosis in systemic lupus erythematosus, respectively. A review of five articles of the use of ESWT in the treatment of osteonecrosis of the femoral head was published by Alves et al. (2009), revealing some favorable results. As mentioned before, ESWT may also be used to treat osteopenia (lower than normal bone mineral density), osteoarthritis (Wang et al. 2012c; Zhao et al. 2012), and osteoporosis (van der Jagt et al. 2009; d'Agostino et al. 2011; Gerdesmeyer et al. 2015b) and has proven its effectiveness in the early stages of the Kienböck disease (disorder of the wrist due to osteonecrosis) (van der Jagt et al. 2009; d'Agostino et al. 2011).

The exact mechanism of shock wave action in cases of osteonecrosis of the femoral head is under research. Extracorporeal shock waves enhance blood supply and new vessel in-growth. They also stimulate osteoblasts and osteogenic differentiation

of mesenchymal stem cells and increase the production of osteocalcin (a noncollagenous protein) (Wang et al. 2004a). Moreover, it has been demonstrated in vitro that ESWT increases mRNA and protein of BMP-2 and induces upregulation of the vascular endothelial growth factor (VEGF) expression in perinecrotic subchondral bone of the femoral head, suggesting neovascularization of the femoral head (Ma et al. 2007, 2008). In vitro studies reported by Yin et al. (2011), exposing bone marrow stromal cells to pressure pulses emitted by an *OssaTron* device (Sanuwave Health, Inc.) showed upregulated VEGF, alkaline phosphatase, RUNX2 (an important protein for osteoblastic differentiation and skeletal morphogenesis), and BMP-2 (a protein involved in development of bone and cartilage) gene expression in bone marrow stromal cells from hips with osteonecrosis through the induction of the NO pathway.

Kusz et al. (2012) reported the results of a prospective study in patients with AVNFH, diagnosed by magnetic resonance imaging (MRI), which received 5 ESWT sessions under X-ray guidance. Each patient had four points marked on the skin above the lesion and was exposed to 1500 shock waves per session (EFD = 0.4 mJ/mm^2) at a rate of 4 Hz. A tensometric platform testing of the strength of the treated limb and an evaluation of the pain intensity and hip function were performed before and up to 12 months after ESWT. The therapy resulted in considerable improvement in the quality of life of the patients 6 weeks post-therapy. At 6 months some patients reported intensified pain and worse hip function; however, these scores were still better than the pretreatment scores.

An article by Vulpiani et al. (2012) reported the effectiveness of ESWT in 36 patients with unilateral AVNFH of different stages. Each patient was exposed to four sessions of 2400 shock waves (EFD = 0.50 mJ/mm^2) at intervals between 48 and 72 h using a *Modulith SLK* shock wave source (Storz Medical AG). Follow-up examinations were performed 3, 6, 12, and 24 months after ESWT. Analyses of the results lead to the main conclusion that ESWT may help to prevent progression of the area of avascular necrosis and manage pain in the early stages of AVNFH. Russo et al. (2015) published their experience in treating more than 600 patients suffering from osteonecrosis of the femoral head with shock waves, also using a *Modulith SLK* shock wave source equipped with radiographic and ultrasound imaging. Their conclusion was that focused shock waves are an effective treatment of osteonecrosis of the femoral head. Efficacy was higher in the initial stages of the disease, and shock waves were more effective than core decompression and bone grafting. Wang and coworkers also reported that ESWT appeared to be more effective than core decompression and nonvascularized fibular grafting in patients with early stage osteonecrosis of the femoral head (Wang et al. 2005, 2012b). The clinical outcomes indicate that shock wave treatment may be considered as the treatment of choice in the early stages of necrosis of the femoral head; however, parameters such as EFD, shock wave rate, and number of shock waves are still to be defined more accurately.

ESWT has also been proposed for the treatment of the bone marrow edema syndrome (BMES), i.e., the accumulation of excessive fluid in certain structures of the bone marrow. It commonly affects the epiphyses of the hip, knee, foot, and ankle,

and may be caused after injury of the bones or due to conditions, such as osteoporosis, avascular necrosis, infection, and tumors. Conventional treatment includes physical therapy, reduced weight-bearing, analgesics, and vasoactive drugs. ESWT may accelerate the resolution of bone edemas and relieve pain; however, a precise diagnosis is mandatory before considering ESWT in cases of bone marrow edema, because the presence of tumor tissue or septic arthritis is a contraindication for shock wave or radial pressure pulse therapy.

d'Agostino et al. (2014) performed a prospective study to evaluate the effectiveness of ESWT in normalizing the symptoms of the BMES of the hip. Their revision included twenty patients that underwent two shock wave therapies (4000 shock waves; EFD approximately 0.5 mJ/mm^2), 48 h apart, using a *Modulith SLK* electromagnetic shock wave source (Storz Medical AG) equipped with ultrasound and radiographic imaging. According to the results, ESWT seems to produce rapid pain relief and functional improvement. In their discussion, the authors hypothesized that the clinical response to ESWT may be due to the nonenzymatic production of NO.

A prospective study to compare the effectiveness of ESWT in normalizing the symptoms of BMES of the knee, with that of intravenously applied prostacyclin and bisphosphonate, was published by Gao et al. (2015). The main conclusion of the report was that ESWT may be an effective and reliable therapy for the treatment of BMES of the knee, producing rapid pain relief and functional improvement. Even if these results are encouraging and demonstrate the progressive regression of bone edema lesions, the methodology is still lacking etiology.

As an example, Fig. 6.19 shows magnetic resonance images of a patient with joint effusion, bone marrow edema, and a defined subchondral insufficiency fracture, before and after ESWT. Shock waves were applied using a *Duolith SD1* shock wave source (EFD = 0.55 mJ/mm^2) with fluoroscopic guidance (Storz Medical AG). The therapy consisted of a single session of 6000 shock waves distributed on the femoral head, 2000 shock waves to the femoral neck area, and 2000 shock waves to the subtrochanteric area. Subsidence of pain was observed promptly, while the patient continued with partial weight-bearing and two canes for 8 weeks. Final magnetic resonance images obtained 58 weeks after ESWT evidenced complete resolution.

6.14 Spasticity

Spasticity, the involuntary resistance to movement, may occur because of several causes, such as a tumor, a stroke, multiple sclerosis, cerebral palsy (permanent movement disorders), or nerve injury, modifying the signals between the nervous system and the muscles. This imbalance leads to increased activity in the muscles. Spasticity negatively affects muscles and joints of the extremities, and is particularly harmful to growing children. It is a combination of paralysis, increased tendon reflex activity and hypertonia, i.e., the reduced capacity of the muscle to stretch. It is estimated that spasticity occurs in up to 38 % of patients poststroke (Watkins et al. 2002).

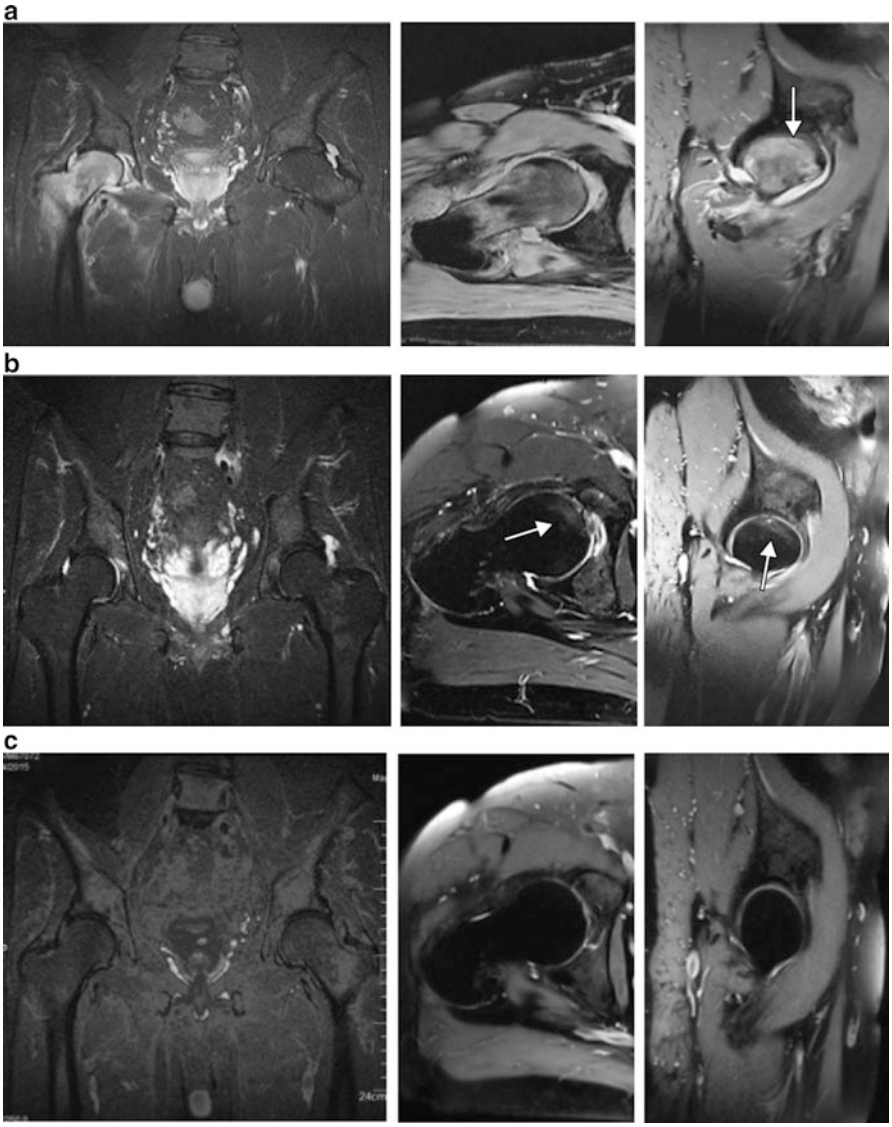


Fig. 6.19 (**a**) Magnetic resonance images of a 71-year-old patient with joint effusion, bone marrow edema from subtrochanteric area up to the femoral head, and a defined subchondral insufficiency fracture (*white arrow*) before ESWT, (**b**) 24 weeks after ESWT showing only a remnant zone of bone marrow edema (*white arrows*) with resolution of joint effusion, and (**c**) 58 weeks after ESWT revealing complete resolution. (Courtesy of L. Guiloff and M. Brañes)

ESWT is considered to be a painless and safe treatment to reduce muscle tone and muscle stiffness in patients suffering from spastic movement disorders. Beneficial effects have been reported to last for several months (Lohse-Busch 2014). The effect of one session of extracorporeal shock waves on muscular dysfunction in

children with spastic movement disorders was reported for the first time by Lohse-Busch et al. (1997). In all therapies, the focus of the shock wave source was maintained outside the patient's body. Each muscle was exposed to 500 shock waves (EFD = 0.06 mJ/mm^2). As a result, the passive range of movement of the patients increased for several weeks.

Manganotti and Amelio (2005) analyzed clinical outcomes of focused shock wave treatments to patients with poststroke spasticity. Various areas of the hypertonic muscles were treated with up to 3200 shock waves (EFD = 0.03 mJ/mm^2) in one session. The passive range of movement increased due to this, but no improvements in the electrophysiological parameters were observed. Several years later, the same authors published a placebo-controlled study of the effect of ESWT on children suffering from cerebral palsy and a leg deformity (unilateral spastic equinovarus foot). A session of 1500 focused shock waves to each of the three main muscles involved (EFD = 0.03 mJ/mm^2) produced evident benefits that persisted during 4 weeks, but disappeared about 12 weeks after ESWT (Amelio and Manganotti 2010). In another study, Manganotti et al. (2012) investigated the effects and safety of ESWT (1600 shock waves, EFD = 0.03 mJ/mm^2) on the peripheral nerve conduction and central conductions from the treated muscles in healthy human subjects. Neurophysiological measures monitored before, immediately after, and 15 and 30 min after ESWT revealed no significant short- or long-term changes in sensory and motor peripheral nerve conduction and in central motor conduction in all the subjects treated.

An example of radial pressure wave therapy to treat spasticity in cerebral palsy (CP) is the randomized, placebo-controlled clinical trial reported by Vidal et al. (2011). A first group of patients received three sessions of 2000 radial pressure waves to each spastic muscle at 1-week intervals. The second group was treated with 4000 radial pressure waves (2000 to the spastic muscle and 2000 to the antagonist muscle). In both groups, the pressure waves (EFD = 0.1 mJ/mm^2) were generated at a frequency of 8 Hz with a *DolorClast* (Electro Medical Systems) at an air compressor pressure of 2 bar. A third group received placebo therapy to the spastic muscles using a sham device with sound generation. The authors concluded that radial pressure wave treatment was more effective than placebo therapy in decreasing spasticity of patients with CP; however, the benefits disappeared approximately 3 months after treatment.

Other authors reported that three sessions of 1500 focused extracorporeal shock waves (EFD ~0.09 mJ/mm^2) generated at 4 Hz with a *PiezoWave* shock wave source (Richard Wolf GmbH), delivered to the medial and lateral *gastrocnemius* (muscle in the back part of the lower leg) were beneficial to stroke patients suffering from hypertonic ankle plantar flexor muscles (Moon et al. 2013). In a prospective open-label study, Santamato et al. (2014) reported that ESWT is safe and efficacious for the treatment of poststroke plantar flexor muscle spasticity. A muscle tone reduction and improved passive ankle dorsiflexion motion was observed after treatment with 1500 shock waves (EFD = 0.1 mJ/mm^2) emitted by an electrohydraulic *EvoTron* shock wave source with an *R20* probe (Sanuwave AG, Lengwil, Switzerland). The duration of the effect depended on the severity of each case. It was long lasting

in patients with echo intensity of calf muscles graded I, II, or III, and brief in subjects with echo intensity graded IV on the Heckmatt scale.

In a prospective, unicenter clinical pilot study, Kim et al. (2013) reported that five sessions of 3000 radial pressure waves (generated at an air compressor pressure of 1.6 bar) were used to treat the spastic *subscapularis* muscles (triangular muscles which are part of the shoulder) in stroke patients. Improvements were observed during treatment sessions; however, the beneficial effects decreased 4 weeks after the last session.

Gonkova et al. (2013) reported the results of an open, controlled, observational study with one placebo treatment session, followed 4 weeks later by one active treatment session, to investigate the effect of radial pressure wave therapy on muscle spasticity of plantar flexor muscles in children with cerebral palsy. Patients (mean age about 5 years) received one treatment (1500 pressure waves at a rate of 8 Hz) to the plantar flexors of the foot using a *BTL-5000* unit (BTL Industries Inc., Columbia, South Carolina, USA) at an air compressor pressure of 1.5 bars. After placebo treatment, no changes measured by clinical or instrumental methods could be observed; however, there was a significant reduction in the spasticity of plantar flexor muscles in pressure wave-treated patients. The improvement remained at the 4-week follow-up. Even if the authors admit that further investigations are required to understand the mechanism causing the observed effects and to confirm their results at long-term follow-up, the reported findings indicate that radial pressure waves could be used for reduction of muscle spasticity in plantar flexors of the lower limbs.

The usefulness of ESWT to treat patients with dystonia (involuntary muscle contractions that cause abnormal postures) was evaluated by Trompetto et al. (2009). Three patients with limb dystonia and three patients with idiopathic writer's cramp (dystonia of the hand) were treated with four sessions (once weekly) of 800–3000 shock waves (0.030 mJ/mm^2) delivered to several areas of the target muscles during each session. An electromagnetic shock wave source (*Modulith SLK*, Storz Medical AG) with in-line ultrasound scanning was used to generate painless shock waves. Clinical evaluation was performed using well-known disability scales. The patients with limb dystonia showed a significant improvement which vanished after approximately 1 month after the last ESWT. Only two patients with writer's cramp showed some improvement. The authors suggest that the beneficial effect of shock waves in patients suffering from dystonia could be a direct effect on fibrosis and other intrinsic components of chronically overactivated muscles by inducing a modulation of the muscle input directed to the spinal cord. However, more trials are required before conclusive recommendations on the use of ESWT in dystonia can be made.

Even if the exact mechanism of shock wave-action on spastic muscles is not yet fully understood, it is known that shock wave and radial pressure wave application has different effects on muscle spasticity than standard vibratory stimulation. A thorough review published by Mori et al. (2014) revealed that shock wave treatment can benefit some patients suffering from muscle hypertonia. Positive results were also observed in children with cerebral palsy after treatment with both focused

shock waves and radial pressure pulses; however, the reduction of muscle tone after ESWT lasted less than 3 months. Focused shock waves have also been used with some success in the upper limb muscles of adult stroke patients. So far no major adverse effect was observed in any of the reported studies. The effect of ESWT combined with botulinum toxin type A (BTX-A) to treat spasticity after stroke, referred to as SBOTE (spasticity treated by botulinum toxin and ESWT) was studied by Santamato et al. (2013). BTX-A, a biologic toxin used to block neuromuscular transmission, is the gold standard therapy for focal spasticity after stroke (Wissel et al. 2009). Even if larger studies are needed to investigate the detailed effects of ESWT on spasticity, the results revealed that BTX-A combined with ESWT was significantly more effective than the combination of BTX-A with electrical stimulation to reduce upper limb spasticity after stroke. The same ESWT dose as applied in previous experimental studies (Amelio and Manganotti 2010) was used.

A limitation to evaluate the effects of shock waves to treat patients suffering from spasticity is an adequate placebo treatment. More information on the treatment of spasticity with focused shock waves and radial pressure waves can be found in the literature (Sohn et al. 2011; Gonkova et al. 2013; Mori et al. 2014).

6.15 Wound Healing

The number of patients having chronic wounds is rising worldwide and the management of soft tissue wounds is still a challenge for specialties, such as dermatology, internal medicine, and angiology. Burn wounds, postsurgical wounds, and posttraumatic wounds are common acute wounds. Chronic wounds include diabetic foot ulcers (DFU), venous leg ulcers, pressure ulcers, and arterial insufficiency ulcers. Wounds are normally defined as chronic if the tissue is not reconstructed after 3 months. Tissue wound healing involves complex cellular and molecular processes. Treatment may include adequate wound bed preparation with surgical and nonsurgical removal of damaged tissue, application of specialized dressings, hyperbaric oxygen therapy (HBOT), negative pressure wound therapy, and ultrasound therapy. As has happened in other areas of medicine, the feasibility to treat soft tissue wounds using shock waves was discovered by chance, during the treatment of bone nonunion (Schaden et al. 2007). The influence of ESWT on the reepithelialization of partial-thickness wounds in piglets was reported long ago by Haupt and Chvapil (1990). Significantly enhanced vascularization of the upper dermis and thicker layer of the newly formed epithelial cells covering the wound was observed after treatment with only ten shock waves generated with an electrohydraulic shock wave source at 14 kV. Application of 100 shock waves, generated at 18 kV resulted in inhibition of the rate of reepithelialization. An increase in vascular flow of ischemic skin and upregulation of proangiogenic genes was reported after extracorporeal shock wave treatment in a murine model (Stojadinovic et al. 2008).

Either defocused or focused acoustical waves have been used to treat delayed/non-healing wounds (Qureshi et al. 2011; Mittermayr et al. 2012; Ottomann et al.

2012; Dymarek et al. 2014). The results suggest that ESWT promotes wound healing with little or no adverse events. Experimental studies revealed an increase in capillary connections and an early downregulation of proapoptotic genes on human microendothelial cells (HMEC) after shock wave application (Sansone et al. 2012). It seems that in most cases unfocused or plane shock waves are more convenient to treat chronic wounds, because they cover a larger area per shock wave, reducing the treatment time and increasing patient's tolerance.

According to the observations by Ottomann et al. (2010), when non-adherent gauze dressings and topical antiseptics are applied to skin graft donor sites, a defocused shock wave treatment (100 pulses/cm^2, EFD = 0.1 mJ/mm^2) with a *OW180C DermaGold* shock wave source (MTS Europe GmbH, Konstanz, Germany) immediately after skin graft harvest can enhance donor site epithelialization. In a relatively small trial, the same group of authors found that a single defocused shock wave treatment to a second-degree burn wound after debridement/topical antiseptic therapy accelerated epithelialization (Ottomann et al. 2012). Furthermore, repetitive ESWT improves skin vascularization to a greater degree than a single therapy.

Kisch et al. (2015) applied fractionated repetitive ESWT (frESWT) in rats to study the effects on microcirculation of the skin. The authors reported that tissue oxygen saturation and blood flow enhanced after the first therapy. These effects increased after a second and third ESWT. Contaldo et al. (2012) quantified the effect of radial pressure wave treatment on murine incisional wound healing. One, three, five, seven, nine, and eleven days after wounding, the animals received 500 radial pressure waves (EFD = 0.1 mJ/mm^2) at a rate of 3 Hz using a *DolorClast* ballistic source (Electro Medical Systems). The microcirculation of the wound was analyzed quantitatively in vivo using epi-illumination intravital fluorescence microscopy. Furthermore, tissue samples were examined ex vivo for wound scoring and immunohistochemistry. The authors concluded that radial pressure wave treatment may facilitate the linear progression of wound healing phases by fostering apoptosis.

Fioramonti et al. (2012) investigated the use of ESWT as a modality for scar treatment in 16 patients with functionally and cosmetically relevant postburn scar contractures or hypertrophic scars. All patients received 100 shock waves per square centimeter (EFD = 0.037 mJ/mm^2) at a pulse rate of 4 Hz twice a week for 6 weeks, without anesthesia or antibiotics, to a limited area of the wound site, using an *EvoTron* electrohydraulic shock wave source with an hand-held therapy head (High Medical Technologies, Lengwil, Switzerland). No bleeding, petechiae, or hematoma occurred during therapy; however some patients felt pain. Photographs were obtained and the VAS was completed before and after therapy. According to the authors, all scars had a better appearance after shock wave treatment, so that ESWT can be considered as a feasible treatment in the management of postburn pathologic scars.

Goertz et al. (2014) analyzed angiogenesis after full-thickness burns inflicted to the ears of hairless mice using three sessions of ESWT. A control group received a burn injury but no ESWT. Group A was exposed to 500 shock waves (EFD = 0.03 mJ/mm^2) on the wound 1 day after burn injury; group B received the same shock wave dose 1 and 3 days after burn injury and group C received ESWT on day one, three,

and seven after burn injury using the same shock wave dose. The shock wave rate was fixed at 1 Hz for all treatments. Shock waves were generated with a modified *Aries Vet* (Dornier MedTech GmbH). Intravital fluorescent microscopy was used to evaluate microcirculatory parameters, angiogenesis, and leukocyte interaction. Mice in the ESWT groups showed accelerated angiogenesis compared to the control group. Two shock wave treatments showed better results than one ESWT and three shock wave sessions showed better results than double ESWT. These results are relevant because infection and septicemia of burn wounds can be prevented by acceleration of wound healing. According to a study published by Kuo et al. (2009), ESWT enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of streptozotocin-induced diabetes.

ESWT has been successful for the management of chronic venous, diabetic, and posttraumatic ulcers, previously treated without success using conservative methods (Saggini et al. 2008). A study on a relatively small patient population, performed by Moretti et al. (2009b) showed that ESWT may be an option in the management of diabetic foot ulceration. Production of granulation tissue with the arrival of leucocytes is characteristic after ESWT. It is associated with enhanced vascular density and increased local blood flow (Arnó et al. 2010). Reduction of the lesion size or complete healing is achieved in several chronic skin ulcers. Defocused pressure sources are used to treat a broad range of vascular lesions.

Wang and colleagues (2009c) published a study concluding that ESWT is more effective than hyperbaric oxygen therapy in chronic DFU. Patients in one group received three shock wave sessions (EFD = 0.11 mJ/mm^2), one every 2 weeks. Patients in another group were subjected to a hyperbaric oxygen therapy daily for 20 days. Photographic documentations, bacteriological examinations, histological studies, immunohistochemical analysis, and blood flow perfusion scans revealed that the shock wave-treated group showed significantly better results than the patients treated with hyperbaric oxygen therapy. Another comparison between ESWT and hyperbaric oxygen therapy in the treatment of chronic DFU revealed increases in immuno-activity expression after ESWT and no significant changes due to hyperbaric oxygen therapy. The treatment dose depended on the size of the ulcer, but at least 500 shock waves (EFD = 0.23 mJ/mm^2) were given per session using a small hand-held *dermaPACE* (Sanuwave Health, Inc.) electrohydraulic shock wave generator, similar to the device shown in Fig. 6.2. The shock wave source was glided over the wound extending 10 mm from the wound perimeter in all directions. The main conclusion of the study was that ESWT showed enhanced angiogenesis and tissue regeneration compared to hyperbaric oxygen therapy (Wang et al. 2011b). Long-term outcomes of ESWT in chronic foot ulcers in a diabetes mellitus group and a non-diabetes mellitus group have also been reported. Clinical assessment for the ulcer status, local blood flow perfusion, and an analysis of mortality and morbidity revealed that ESWT appears to be efficient in the treatment of both chronic diabetic and non-diabetic foot ulcers. Even if the blood flow perfusion rate increased after treatment for up to one year, it decreased after one year of shock wave application in both groups; however, non-diabetic patients showed significantly better blood flow perfusion than diabetic patients after five years. In the diabetic

group, complete healing was observed after five years in 43 % of the ulcers. In the non-diabetic group, the percentage of healed ulcers after five years was 71 %. Shock waves were applied using a *dermaPACE* shock wave source (Sanuwave Health, Inc.) and the methodology mentioned above (EFD = 0.11 mJ/mm^2) (Wang et al. 2014).

The efficacy of ESWT on healing in chronic DFU was also studied by Omar et al. (2014). In the ESWT group ($n = 24$) each ulcer received 100 pulses per square centimeter (EFD = 0.11 mJ/mm^2) twice per week for a total of eight treatments. Therapy efficiency was assessed by the reduction in the wound surface area. The average healing time was significantly lower in the ESWT-group compared with the control group. All treated ulcers had a reduction in wound size, with no adverse reactions.

In a thorough review on ESWT for wound healing, Mittermayr and colleagues concluded that shock waves induce complex biological responses involved in enhanced tissue perfusion and angiogenesis. Advantages of ESWT are that it is easy to perform, allows treatment in an outpatient setting, and does not require anesthetics. According to their review, promising data for the treatment of difficult to heal wounds has been reported. ESWT may be a valid alternative to conservative and surgical treatments in patients with chronic wounds; however, well-designed studies with large number of patients to confirm the reported findings are still needed (Mittermayr et al. 2012).

Qureshi et al. (2011) reported the results of reviewing the literature using an evidence-based approach. According to their findings, clinical trials are encouraging for the use of ESWT in the treatment of wounds, inducing mechanotransduction and immunomodulation. Reports of serious complications were not found; however, there was no consensus on which EFD, frequency, number of pulses, and pressure waveforms are optimal and which type of wounds are most likely to benefit from ESWT.

To improve ESWT for wound healing, Weihs et al. (2014) analyzed whether shock wave treatment influences proliferation by altering major extracellular factors and signaling pathways involved in cell proliferation. Their in vitro and in vivo study included several cell types and demonstrated that ESWT promotes wound healing by the release of cellular adenosine triphosphate (ATP) and P2 receptor activation that promotes tissue remodeling via extracellular signal-regulated kinase ½ (Erk1/2) activation. (ATP is a molecule used by enzymes and proteins in several cellular processes, such as biosynthetic reactions and cell division). The results of this study could also help to explain the non-responsiveness to ESWT in some patients suffering wound healing disorders. Since the Erk1/2 signaling pathway is crucial in wound healing processes, the authors hypothesized that non-responding patients might have an impaired Erk1/2 signaling pathway.

Antonic et al. (2015) recently evaluated the in vitro effects of 100 shock waves (EFD = 0.1 mJ/mm^2, shock wave rate = 1 Hz) on the keratinocyte morphology, cytoskeleton, and mitotic activity. Shock waves were generated by an *OW180C DermaGold* electrohydraulic shock wave source (MTS Europe GmbH). Hematoxylin and eosin staining, immunohistochemistry for Ki-67, CK5, CK14, and CK10 were performed. No alterations of the monolayer of cells could be observed.

When assessing histological images of shock wave-treated and untreated (control) cells, no morphological differences could be seen between groups. The authors concluded that shock wave-treated keratinocyte cell cultures showed increased keratinocyte proliferation and that ESWT promoted differentiation of the keratinocyte towards basal-layer-like morphology.

A systematic review of the literature, performed by Dymarek et al. (2014) to evaluate evidence of ESWT effectiveness, revealed that ESWT is generally applied once or twice a week. The total number of sessions varied between three and six. The EFD levels range between 0.03 and 0.25 mJ/mm^2, being 0.1 mJ/mm^2 the most commonly used energy flux density. In most studies 10–500 pulses/cm^2 of wound area were applied per session. The reported results included wound closure and reepithelialization, enhancement of tissue granulation, reduction of necrotic fibrin tissue, improvement of blood flow perfusion, and less need of antibiotics. Statistically significant differences in rates of wound closure, compared to standard therapies, including hyperbaric and sham ESWT, were reported. Based on this review, which comprised articles published between the year 2000 and 2013, ESWT can be considered as a safe and mostly painless wound treatment modality; nevertheless, evidence-based practice guidelines still have to be developed.

Notarnicola et al. (2014) also have been successful in the management of neuropathic ulcers of the foot. The authors used focused shock waves (EFD = 0.03 mJ/mm^2) generated with a *Minilith SL1* (Storz Medical AG). Their protocol consisted of three sessions at 3–7 day intervals. The results of two studies, i.e., two shock wave doses, were compared: 100 shock waves per square centimeter of lesion area, and 200 shock waves per square centimeter of lesion area. In both studies the reepithelialization rate, expressed in mm^2/day, was significantly higher in the ESWT group compared with the control group. Interestingly, the lower dose (100 shock waves/cm^2) was significantly more efficient than the higher shock wave dose.

A review to investigate the effectiveness of ESWT for the treatment of lower limb ulceration associated with comorbidities, such as diabetes, peripheral vascular disease, and venous insufficiency, was published by Butterworth et al. (2015). Cases where the ulcer was associated with surgical complications, pressure sores, or burns were excluded. A trend to suggest that ESWT improves wound healing was identified; however, the lack of standardization was of concern considering the non-blinded design of the studies. Furthermore, treatment protocols varied between studies, making comparison difficult. The authors commented that to reduce bias it is essential that rigorous RCT methods are used. Outcome measures should include detailed information about the criteria used to identify the presence of lower limb ulceration. According to the authors, there is limited evidence to support ESWT as a treatment for lower limb ulceration. After reviewing clinical outcomes, Wang and coworkers (2015b) found that ESWT appears to be effective in the treatment of DFU. Compared to other therapy modalities, ESWT is cost effective, practically without undesired side effects and seems to be a good alternative when conventional treatment methods fail (Fig. 6.20). As in other applications, the optimal number of pressure waves, the delivery rate, the number of sessions, and the timing have to be determined based on larger series of randomized controlled clinical trials.

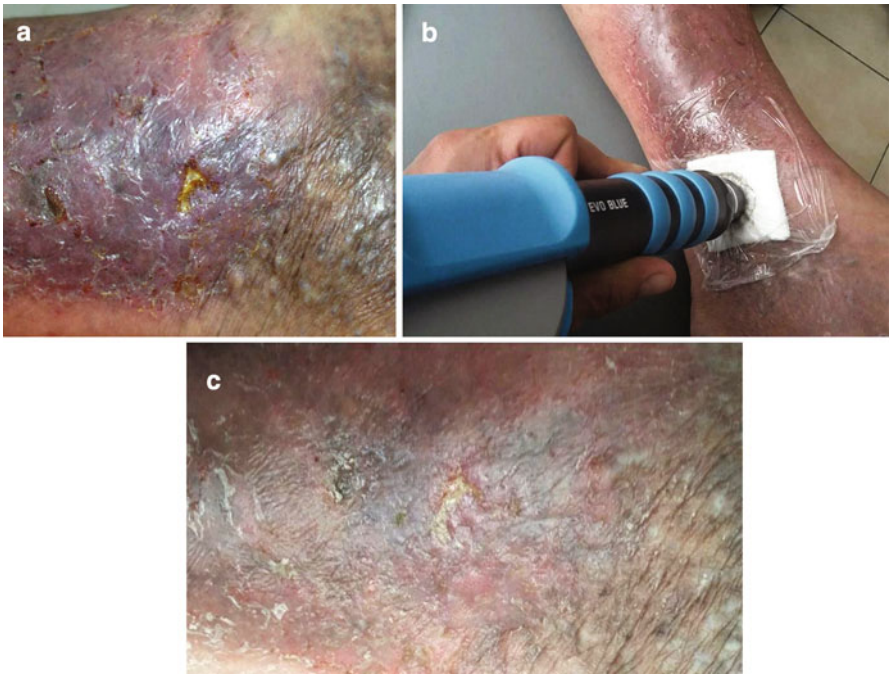


Fig. 6.20 A small venous ulcer in a 54-year-old patient (**a**) before, (**b**) during, and (**c**) nine days after three sessions of 2000 radial pressure waves generated at an air pressure of 4 bar and a delivery rate of 8 Hz with an *Evo Blue* device (Electro Medical Systems, Nyon, Switzerland). No antibiotics were administered. (Courtesy of L. Parada)

6.16 Aesthetic Dermatology

Cellulite is the formation of irregular skin with clusters of fat cells that commonly occurs on the thighs and buttocks affecting most post-adolescent women. Its appearance depends on several factors, such as genetic predisposition, body weight, age, diet, and hormonal changes. In the medical field it is known as *gynoid lipodystrophy*, *adiposis edematosa*, *dermopanniculosis deformans*, and *status protrusus cutis*. Available therapeutic modalities are only partially effective. Novel treatments are continuously being developed; however, often with a lack of understanding of the phenomena involved. Information on the etiology, treatment modalities and pathophysiology of cellulite can be found in the reviews published by Khan et al. (2010a, 2010b), Gold (2012), and by de la Casa and colleagues (2013).

These days, ESWT and rESWT are considered alternatives that can improve the clinical picture by one cellulite grade or more. Cellulite grades are determined by clinical evaluation. Further aids to classify cellulite are contact thermography, measurement of the skin blood perfusion, contrast photography, as well as recoil and elasticity measurements. In aesthetic dermatology, the term *acoustic wave therapy*

(AWT) has become popular and has been used as a synonym for both ESWT and rESWT. Scars, striae, fibrosis, and *lipedema* (adipose tissue generally affecting the legs) have been treated successfully with pressure pulses. Furthermore, AWT is also used after liposuction (Adatto et al. 2014).

An early study published by Siems et al. (2005) revealed that ESWT performed on 26 females suffering from lipedema and/or cellulite improved significantly the biomechanic skin properties leading to smoothening of the dermis and hypodermis surface. It was also concluded that a release of lipid peroxidation products from edematous dermis is an important sclerosis-preventing effect of ESWT in lipedema and cellulite. The authors used a modified *DermaSelect* pressure wave source (Storz Medical AG). For this study an EFD of 0.16 mJ/mm^2 (30 mm behind the focus) was used. Each patient was subjected to six sessions consisting of 1000 shock waves to one thigh (always the same). Additionally, complex physical decongestive therapy (CPDT) was carried out at both thighs daily. According to an article by Angehrn and colleagues (2007), early studies of low-energy defocused shock waves applied onto cellulite afflicted skin at the lateral thigh of 21 female patients twice a week for 6 weeks showed remodeling of the collagen within the dermis. High-resolution ultrasound performed before and after ESWT was used to evaluate treatment outcome. The skin was exposed to pressure pulses produced by an electrohydraulic *ActiVitor Derma* (SwiTech Medical AG, Kreuzlingen, Switzerland) shock wave source (EFD=0.018 mJ/mm^2). On each side, the treated area was divided into squares of approximately 4 cm^2 that received 100 pressure pulses each. The same group reported the effects of four ESWT sessions to a 50-year-old female patient with cellulite grade 3 (Kuhn et al. 2008). A total of 800 pressure waves were applied per session on a 20 per 20 mm sample with an *ActiVitor Derma* device (EFD=0.155 mJ/mm^2) at a rate of 4 Hz. Skin samples for histopathological analysis were taken from the treated and from the contra-lateral untreated area. The analysis showed no damage to the treated skin tissue, but induction of neocollageno- and neoelastino-genesis.

Another representative cohort article, published by Christ et al. (2008), reports results after treating 59 women with six to eight sessions consisting of 3200 pressure waves (EFD=0.25 mJ/mm^2) generated with a *CellActor SC1* (Storz Medical AG). Ultrasound was used to evaluate changes in the connective tissue. Skin elasticity values improved significantly. Increased density and firmness in the network of collagen/elastic fibers in the dermis and subcutis could be observed, especially in patients with a long history of cellulite.

A randomized trial on the efficacy of radial pressure wave therapy for an improvement in the appearance of cellulite was performed by Adatto and colleagues (2010) with 25 females. Six sessions of 3000 pulses (air compressor pressure between 2.6 and 3.6 bar) at a repetition frequency of 15 Hz were applied on a 10 by 15 cm rectangle on a single leg, using a *D-Actor 200* (Storz Medical AG). Skin depressions, elevations, roughness, and elasticity were evaluated. The authors reported a statistically significant difference between treated and untreated legs after six sessions. The same authors published a study of 14 females treated with eight sessions of 1500 radial pressure waves (EFD between 0.45 and 1.24 mJ/mm^2) generated with a *CellActor SC1* (Storz Medical AG) using an air compressor pressure between 3 and

4 bar (Adatto et al. 2011). A significant reduction in the subcutaneous fat layer thickness and the averaged circumference of the thighs could be demonstrated.

Tinazzi et al. (2011) published the results of pressure wave therapy to reduce endothelial cell damage and skin fibrosis in 30 patients with progressive systemic sclerosis (SSc), i.e., thickening of the skin due to accumulation of collagen. An evaluation of the patient's skin rated by a clinical palpation called Rodnan Skin Score (RSS) and the VAS for skin wellness were performed before, immediately after, and at 7, 30, 60, and 90 days after the treatment. Sonographic examination of the patients' arms was performed, and blood samples were obtained before and at different times after treatment. A rapid and persistent reduction of RSS, a decrease of the VAS, a more regular skin structure, and an improvement in skin vascularization were observed; however, there was no difference in skin thickness before and after therapy. The authors also reported that endothelial progenitor cells and circulating endothelial cells increased, while serological biomarkers showed no variation before and after treatment.

A single-center, double-blinded, randomized-controlled trial, including 53 patients by Knobloch et al. (2013) showed that six sessions (one per week) of 2000 pressure pulses at 0.35 mJ/mm^2 with a *Duolith* (Storz Medical AG) in combination with gluteal strength training had significantly better outcomes in moderate to severe cellulite than sham ESWT combined with gluteal strength training. The control group received the same number of sessions and pulses at an EFD of 0.01 mJ/mm^2. The evaluated outcome parameter was the photo-numeric cellulite severity scale (CSS). Direct effects on the associated lymphedema, dermal revitalization, enhanced skin elasticity, and smoothness by disruption of fat components seemed to be responsible for the positive results (Bae and Kim 2013). Russe-Wilflingseder and colleagues (2013) published the results of a placebo-controlled double-blinded, prospectively randomized clinical study with 17 patients treated once a week for 7 weeks with a *D-Actor 200* (Storz Medical AG) radial pressure wave source. The outcome was evaluated at different times before, during, and after therapy. Results revealed that ESWT reduced the circumference, the number and the depth of dimples, and enhanced skin firmness, texture, and shape.

In a prospective, single-center, randomized study, Schlaudraff et al. (2014) demonstrated that radial pressure waves (air compressor pressure between 3.5 and 4.0 bar, frequency 15 Hz) generated with a *DolorClast* (Electro Medical Systems) are effective to treat cellulite. Patients were treated unilaterally by distributing 15,000 pressure pulses homogeneously over the posterior thigh and buttock area. The therapy included two sessions per week for 4 weeks. Treatment outcome was evaluated after the last treatment and 4 weeks later. The therapy was well tolerated by all patients and no unwanted side effects were observed. The authors also reported that, according to their results, clinical outcomes cannot be predicted by the patient's initial cellulite grade, weight, height, body mass index (BMI), or age. Cellulite grades were documented by digital photography and determined by clinical inspection and by contact thermography.

Nassar et al. (2015) published the results of a randomized controlled trial with an intraindividual control applying 1500 focused shock waves per leg (EFD between 0.56 and 1.24 mJ/mm^2) followed by 3000 radial pressure pulses on the same leg,

generated at an air compressor pressure between 2.6 and 5.0 bar and a rate of 16 Hz. The whole treatment consisted of eight sessions twice a week. A reduction in both thigh circumference and subcutaneous fat layer thickness, measured through ultrasound, was observed 12 weeks after the last session.

Cryolipolysis is a noninvasive procedure for reducing subcutaneous fat and fibrous cellulite. The method damages subcutaneous adipocytes, with no effects on lipid or liver marker levels in the bloodstream. Combining radial pressure pulses and cryolipolysis has been effective in causing death and slow resorption of destroyed adipocytes. Ferraro et al. (2012) managed to significantly diminish the fat thickness of 50 patients with localized fat and cellulite using both a freezing probe for localized fatty tissue and a ballistic radial pressure wave source to treat fibrous cellulite. The gradual reduction of fat tissue was confirmed by histologic and immunohistochemical analysis. A significant improvement in microcirculation was also observed. For some patients, this therapy called *ice-shock lipolysis* could be an alternative to liposuction.

As mentioned in Sect. 4.13, Kiessling et al. (2015) exposed chicken embryos *in ovo* to various doses of radial pressure waves and found a dose-dependent increase in the number of embryos that died after treatment. Some embryos that survived had severe congenital defects. Even if these results cannot be directly extrapolated to human embryos, rESWT and ESWT should only be used to treat cellulite if pregnancy is ruled out.

After a meta-analysis that included eleven published clinical studies, Knobloch and Kraemer (2015) found substantial body of evidence that both focused shock waves and radial pressure waves improve cellulite; however, so far there is no consensus on optimal treatment protocols, because the published trials vary in terms of the devices, number of sessions, follow-up periods, physical parameters (EFD, number, rate, and waveform of the pressure pulses), and evaluation methods used. Typically six to eight sessions once or twice a week were performed. Side effects were rare. They included light pain, sore muscles, skin reddening, and hematomas. Main contraindications were pregnancy, the use of anticoagulants, coagulation disorders, thrombosis, tumor diseases, and cortisone therapy 6 weeks or less before treatment (Adatto et al. 2014). So far, follow-up information beyond one year is not available. More clinical studies are still needed to determine how the treatment modality, the pressure profile, and the EFD, as well as other parameters, such as the patient's age, BMI, and the stage of the cellulite influence the treatment outcome.

In the near future, it is to be expected that shock waves and radial pressure waves will be popular to treat an increasing number of different indications in aesthetic dermatology. The treatment of capsular fibrosis after aesthetic breast implant augmentation with planar shock waves may be an example. In a cross-sectional study, Heine and colleagues (2013) treated a total of 19 cases of capsular fibrosis after insertion of mammary implants, using a *Duolith SD1* (Storz Medical AG). The therapy consisted of an average of eight sessions of 1000–1500 shock waves each (EFD between 0.22 and 0.38 mJ/mm^2). The therapy was well-tolerated and easy-to-use. Patients who had undergone a breast reconstruction after mastectomy did not report a significant pain reduction; however, patients who received aesthetic breast augmentation reported pain alleviation.

6.17 Heart Diseases

Coronary artery disease (CAD) or *ischemic heart disease* is the first cause of death in developed countries. It occurs when the arteries supplying oxygen-rich blood to the heart muscle buildup plaque on their inner walls, getting harder and narrower (atherosclerosis). The plaque generally consists of calcium phosphates, fatty deposits, cholesterol, and abnormal inflammatory cells. The muscle cells of the heart (myocytes) die from the lack of oxygen and get replaced by fibrous tissue that forms a scar. The scar has different properties as healthy myocardium, leading to a decreased heart function. Risk factors that contribute to myocardial infarction (MI) include hypertension, smoking, high blood cholesterol levels, overweight, and diabetes. Drug therapy, percutaneous coronary intervention (PCI), transmyocardial laser revascularization (TMR), and coronary artery bypass grafting (CABG) are the common management options. Unfortunately, these techniques are invasive and associated with considerable risks. Extracorporeal shock wave application, in this case also called *cardiac shock wave therapy* (CSWT), is an approach to ameliorate myocardial ischemia and improve cardiac function by promoting angiogenesis and revascularization (Khattab et al. 2007; Stojadinovic et al. 2008; Davis et al. 2009; Ito et al. 2009; Zimpfer et al. 2009; Gutersohn et al. 2000; Kikuchi et al. 2010; Wang et al. 2010, 2012a). The initial human treatments were performed in 1998 (Caspari and Erbel 1999). Today, CSWT is considered as a therapy for chronic stable angina pectoris (Schmid 2014).

The *Modulith SLC* (Storz Medical AG) was the first commercial shock wave source used to treat ischemic zones of the heart muscle, generating neo-angiogenesis and increasing blood circulation without anesthesia. Shock waves are emitted during the refractory phase of the cardiac cycle. Even if the shock wave generator has similarities with sources used in SWL, the focal distance and aperture were specially designed for its use in cardiology. This is crucial because of the proximity of the lungs. Precise targeting is achieved using in-line ultrasound localization. The cylindrical electromagnetic shock wave source (Sect. 5.3.2) offers a penetration depth between 0 and 150 mm. As shown in Fig. 6.21, the shock wave source is mounted on a mobile arm to adjust the beam axis according to each specific case.

In vivo studies revealed that shock wave-induced acoustic cavitation acts on myocardial and vascular endothelial cells. A report that demonstrated the usefulness of ESWT as a treatment of chronic myocardial ischemia in pigs using a well-known model to examine angiogenic therapies in the ischemic myocardium was published by Nishida et al. (2004). The technique is based on placing a constrictor around the proximal left circumflex coronary artery to induce a total occlusion of the artery without causing myocardial infarction (O'Konski et al. 1987). Shock waves (EFD = 0.09 mJ/mm^2) were applied to nine spots (200 shock waves per spot) in the ischemic region using a Storz Medical AG shock wave source 4 weeks after the implantation of the constrictor. ESWT was repeated three times within 1 week. Pigs in the sham group received the same anesthesia procedures but without shock wave treatment. Only shock wave-treated pigs developed coronary collateral vessels in the ischemic region, and an increased number of visible coronary arteries.

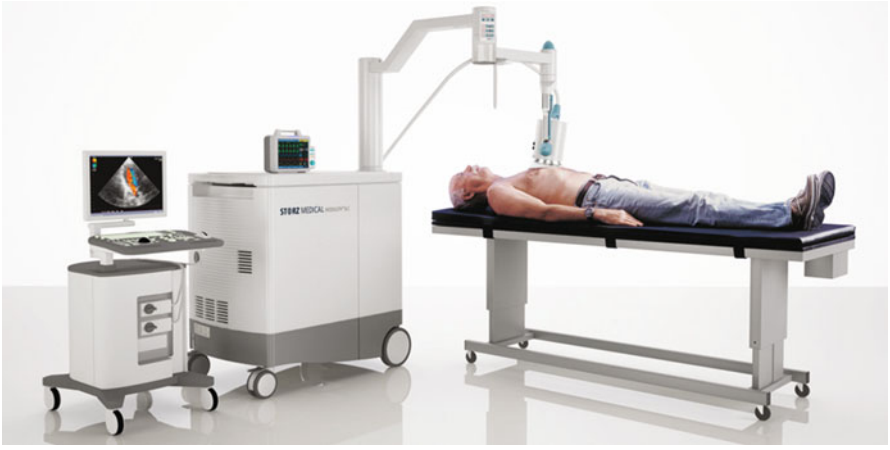


Fig. 6.21 Photograph of the *Modulith SLC* electromagnetic shock wave source (Storz Medical AG, Tägerwilen, Switzerland) with in-line ultrasound localization, designed for noninvasive cardiac revascularization

Further studies indicating that extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs were published by Uwatoku et al. (2007).

In vitro experiments on adult resident cardiac primitive cells isolated from bioptic fragments of normal human hearts and from explanted pathologic hearts with post-ischemic cardiomyopathy by Nurzynska et al. (2008) demonstrated that shock waves have a positive effect on both the proliferation and the differentiation of cardiomyocytes, smooth muscle, and endothelial cell precursors. Shock waves were generated using a *Modulith SLK* (Storz Medical AG) and coupled into the culture dish containing adherent cells by means of a water-filled cushion covered with ultrasound gel. The cells were plated at a density of 15×10^3 cells/cm^2, subjected to 800 shock waves (EFD = 0.1 mJ/mm^2), and cultured for 7 days. Culture dishes containing the same number of non-shock wave-treated cells served as a control. The results suggested that ESWT could inhibit or retard the pathologic remodeling and functional degradation of the heart if applied during the early stages of heart failure.

Positive effects of epicardial shock wave therapy in a rodent model of ischemic heart failure were studied by Zimpfer and colleagues (2009). According to their study, epicardial application of shock waves improved left ventricular function and decreased serum levels of B-type natriuretic peptide. Additionally, significant upregulation of mRNA levels of the VEGF were observed. These studies were followed several years later by an evaluation of the safety and efficacy of epicardial shock wave treatment in pigs published by the same research group (Holfeld et al. 2014b). Myocardial infarction was induced by left anterior descending artery ligation. Four weeks later, the pigs underwent re-thoracotomy with 300 epicardial shock waves (EFD = 0.38 mJ/mm^2) applied to the infarcted anterior wall. Six weeks after

treatment, the left ventricular ejection fraction (LVEF) improved in the shock wave group, whereas no improvement was observed in the control group. A significant angiogenesis was revealed by quantitative histology in the shock wave-treated pigs. No adverse effects were reported.

Whether ESWT ameliorates left ventricular (LV) remodeling after myocardial ischemia-reperfusion injury was studied by Ito et al. (2010) in pigs in vivo. Thirty pigs were subjected to an ischemia and reperfusion for 90 min using a balloon catheter. The animals in the ESWT group ($n = 15$) were treated three times in 1 week with 200 shock waves (EFD = 0.09 mJ/mm^2) per spot at different spots around the infracted myocardium with guidance of an echocardiogram equipped within a specially designed electromagnetic shock wave generator (Storz Medical AG). One month after ischemia-reperfusion, the shock wave-treated pigs showed significantly ameliorated LV remodeling in terms of LV enlargement, reduced LV ejection fraction, and elevated LV end-diastolic pressure. Compared with the control group, the animals in the ESWT group showed increased regional myocardial blood flow, capillary density, and endothelial nitric oxide synthase activity.

Fu and coworkers (2011) utilized a mini-pig ischemic heart model to demonstrate that ESWT increases endothelial progenitor cells, enhances angiogenesis, and reduces inflammatory response, oxidative stress, cellular apoptosis, and fibrotic changes in ischemic LV myocardium. They also reported that shock waves reversed ischemia-related left ventricular dysfunction and attenuated ischemia induced left ventricular remodeling without side effects.

In 2006 extracorporeal cardiac shock wave therapy was reported to ameliorate myocardial ischemia in patients with severe CAD by Fukumoto et al. (2006). The report was followed by clinical trials of cardiac shock wave therapy in nine patients with end-stage ischemic heart disease with no indication of PCI or CABG. The therapy consisted of 200 shock waves at an EFD of 0.09 mJ/mm^2, three times a week generated with a cylindrical coil electromagnetic shock wave source (Storz Medical AG). The therapy improved symptoms and reduced nitroglycerin use as well as myocardial perfusion. The shock wave-induced effects persisted for at least 12 months. No complications or adverse effects were observed (Shimokawa et al. 2008; Shimokawa and Ito 2010). A double-blind and placebo-controlled study by Kikuchi et al. (2010) further demonstrated the effectiveness and safety of ESWT to treat patients suffering from severe angina pectoris. Nine ultrasound-guided shock wave sessions (between two and three treatments per week) were scheduled. The efficacy and safety of ESWT in patients with advanced CAD was also reported by Wang et al. (2010) on a small patient population.

Kazmi et al. (2012) studied the effects of three ESWT sessions per week on the first week of each month, during 3 months, in improving the clinical condition among patients with advanced CAD. About 300 shock waves were applied to the ischemic area per session (EFD = 0.09 mJ/mm^2). The results demonstrated a significant improvement in shock wave-treated patients compared with non-shock wave-treated patients.

In another study, Yang and colleagues (2013) tested the effectiveness of shock wave therapy for patients with coronary heart disease in a randomized, double-blind,

controlled clinical trial. Fourteen patients were assigned to the shock waved-treated group and 11 to the control group. The treatment consisted of nine sessions during 3 months. Shock waves were applied with a *Modulith SLC* electromagnetic shock wave source (Storz Medical AG), equipped with a real-time ultrasound probe (Fig. 6.21). The EFD was gradually increased up to 0.09 mJ/mm^2. Therapy outcomes were assessed by the New York Heart Association (NYHA) classification, the Canadian Cardiovascular Society (CCS) angina scale, the Seattle angina questionnaire (SAQ) scale, the 6-min walking test, the nitroglycerin dosage, as well as rehospitalization rate, and mortality. The main conclusion of the study was that CSWT significantly improved the clinical condition, perfusion, and metabolism of the ischemic myocardium and myocardial contractive function. No complications from the shock wave therapy were observed.

The effects of shock wave-induced myocardial revascularization on clinical symptoms as well as LV function in 20 patients with refractory angina were reported by Zuoziene and colleagues. Extracorporeal shock waves were applied with a *Cardiospec* shock wave source (Medispec Ltd., Germantown, Philadelphia, USA) under echocardiographic guidance (EFD between 0.03 and 0.2 mJ/mm^2). The therapy consisted of three groups of three sessions per week, scheduled every 4 weeks. Up to 500 shock waves (R-wave-triggered) were delivered per session. Left ventricular function was assessed by MRI before and 6 months after ESWT. Clinical results showed both a significant clinical response and improved left ventricular ejection fraction in all patients (Zuoziene et al. 2012).

Another study on the efficacy of ESWT in myocardial revascularization in patients with refractory angina pectoris was published by Cassar et al. (2014). The authors performed a prospective trial on 15 patients with medically refractory angina and no revascularization options. All patients were treated at three zones during nine ESWT sessions applying 100 shock waves (EFD = 0.09 mJ/mm^2) to each ischemic area per session using a *Cardiospec* shock wave generator (Medispec Ltd.). The efficacy was evaluated by treadmill tests, as well as ischemic burden on pharmacological single-photon emission computed tomography (SPECT) 4 months after the last ESWT. There was a statistically significant increase in exercise treadmill time from baseline to last follow-up after the treatment. The authors concluded that ESWT seems to be an efficient treatment for patients with refractory angina pectoris.

The results of a prospective, randomized trial indicating that low-energy shock wave therapy improves wound healing after vein harvesting for coronary artery bypass graft surgery were published by Dumfarth et al. (2008). A significant difference in the incidence of complications between shock wave and non-shock wave-treated patients was detected. It is interesting that according to results obtained by Mittermayr and colleagues (2011), the increase in vascular flow after ESWT is irrespective of the application time, that is, it does not depend on whether the treatment was given before or after ischemia.

Because ESWT is limited to certain areas of the heart, direct epicardial shock wave therapy (DESWT) was developed as an alternative. The methodology has shown promising results in pre-clinical and clinical pilot trials applied during

CABG (Holfeld et al. 2015). The main advantage is that the whole heart can be treated with shock waves resulting in a marked functional improvement of the heart; however, since the method is invasive it can be used for CABG patients only (Zimpfer et al. 2009; Holfeld et al. 2014b, 2015).

The exact mechanism of angiogenic and regenerative action remains unknown. A study reported by Holfeld et al. (2016) revealed a crucial role of the innate immune system, namely Toll-like receptor 3, to mediate angiogenesis upon release of cytoplasmic RNAs by mechanotransduction. Larger studies are still needed to better define the optimal methodologies and the clinical effectiveness of ESWT to treat heart diseases.

6.18 Chronic Pelvic Pain Syndrome

In urology, *chronic pelvic pain syndrome* (CPPS), characterized by urinary and erectile dysfunction, pain in the prostate, perineal, inguinal, scrotal, or suprapubic pain, is a frequent outpatient diagnose of increasing incidence in the western world, with an incidence around 15 %; however, its pathophysiology has not been satisfactorily explained (Nickel 2003; Pontari and Ruggieri 2004; Duloy et al. 2007; Shoskes et al. 2008; Parker et al. 2010). Most patients suffer the non-bacterial form of CPPS. Some medical therapies that have been used with relatively low effectiveness are anti-inflammatory agents, α-receptor blockers, antibiotics, and 5α-reductase inhibitors (Anothaisintawee et al. 2011). Other alternatives include acupuncture, electromagnetic treatment, physiotherapy, trigger point massage, thermotherapy, and intraprostatic injections. The role of the prostate in the CPPS is questionable, because a significant degree of chronic pelvic pain has also been reported to occur in women (Marszalek et al. 2008).

Shock waves have been proposed by several authors as a therapy for patients with CPPS (Zimmermann et al. 2005; Zimmermann and Janetschek 2010). The results of two groups of patients with prostatitis and no evidence of bacteria in urinary and seminal culture tests, exposed to shock waves using a perineal approach, were reported by Zimmermann et al. (2008). The first group was treated with six sessions of 2000 shock waves at a rate of 3 Hz and an EFD of 0.11 mJ/mm^2 within 2 weeks. Shock waves were generated by a *Minilith SL1* (Storz Medical AG). Using the integrated ultrasound imaging system, the focal zone of the shock wave source was moved to scan the whole prostate. The second group of patients received one treatment of 3000 impulses (EFD=0.25 mJ/mm^2) weekly for 4 weeks using a *Duolith SD1* (Storz Medical AG). In this group no ultrasound imaging was used. Reported pain reductions according to the chronic prostatitis symptom index (CPSI) and the VAS were statistically significant in both groups. The voiding conditions improved temporally but with no statistical significance. A limitation of this report was the lack of a control group. In a following study, Zimmermann and colleagues (2009) included a placebo group. Patients in this control group were treated with the same shock wave source; however, shock wave coupling was blocked by a shock wave-absorbing material. ESWT

patients were treated four times (one treatment per week) with 3000 shock waves at a rate of 3 Hz (EFD = 0.25 mJ/mm^2) using a *Duolith SD1* without anesthesia. All patients in the shock wave-treated group showed a statistically significant improvement of pain and voiding conditions in comparison to the control group. The same year, Marszalek and coworkers (2009) reported level 1 evidence (evidence from a review of the relevant RCTs) for ESWT in patients with CPPS.

A randomized sham-controlled trial to evaluate the efficacy of shock waves on CPPS was conducted by Vahdatpour and colleagues (2013). Each patient received one session of 3000 pressure pulses (EFD = 0.25 mJ/mm^2) per week at a shock wave rate of 3 Hz during 4 weeks in supine position with a *Duolith SD1* shock wave source (Stroz Medical AG). The position of the probe was verified by means of transperineal ultrasound after each 500 pulses. The EFD was increased by 0.5 mJ/mm^2 in each session. A sham group received the same protocol; however, the shock wave generator was turned off. Evaluations were done 1, 2, 3, and 12 weeks after the first treatment or sham treatment. Pain was determined with the VAS and the National Institute of Health (NIH) chronic prostatitis symptom index (NIH-CPSI). Due to the placebo effect, improvement was reported in both the treated and the sham group; however, a significant improvement could be detected for the ESWT group after the second week. Even if the authors concluded that the shock wave therapy is safe and effective to treat CPPS patients, they also admitted that long-term follow-ups are still required.

In 2014 another group evaluated the effect of ESWT on CPPS due to non-bacterial prostatitis in a long-term period. Forty patients with CPPS were distributed into the ESWT or the sham group and evaluated at 16, 20, and 24 weeks. A total of 3000 shock waves were applied once a week for 4 weeks at a rate of 4 Hz. The initial EFD of 0.25 mJ/m^2 was increased each week. Patients in the sham group received the same protocol, however, with the shock wave source being turned off. The main conclusion of the authors was that although shock wave treatment is safe and effective in the short-term, its long-term efficacy was not supported by their study (Moayednia et al. 2014).

After analyzing the current treatment indications and the scientific background, Zimmermann (2013) concluded that ESWT has a significant importance in the therapy of CPPS because of placebo-controlled proven positive results, straightforwardness of its clinical application, lack of side effects, little time and personnel expenditure, and local application to the affected region.

Due to the relative success of ESWT to treat patients suffering from CPPS, shock wave therapy has also been suggested in the treatment of pain associated with interstitial cystitis (IC), i.e., inflammation of the submucosal and muscular layers of the bladder. Kabisch and Fahlenkamp (2013) reported the treatment of 13 patients with electro motive drug administration (EMDA) and ESWT, resulting in an increase in bladder capacity and pain relief for several months. (EMDA is a means of using pulsed direct current to improve the delivery of substances into the body.) The patients received shock wave treatment (EFD between 0.25 and 0.35 mJ/mm^2) applied both suprapubically and from the perineal region at weekly intervals. A total of 3000 shock waves were applied to each site at a frequency of 4 Hz. In most cases, intervals between treatments were 3–6 months.

6.19 Peyronie's Disease

Shock waves have been used successfully for patients suffering from *Peyronie's disease* (PD) also known as *induratio penis plastica* (IPP) or *chronic inflammation of the tunica albuginea* (CITA), that is, the growth of inelastic fibrous plaques in the penis (Zimmermann 2013). PD is an acquired connective tissue disorder that alters the penile anatomy. The disease affects about 5 % of men. ESWT may reduce fibrotic plaque and penile curvature as well as pain on erection (Butz and Teichert 1998; Hauck et al. 2000; Lebret et al. 2002). Shock waves are coupled into the flaccid penis and focused on the plaque. The procedure does not require anesthesia. A hypothesis is that shock waves induce an inflammatory reaction by increasing the vascularity, breaking down the plaque. Even if initial results were promising, other authors reported that shock waves showed to be beneficial on painful erections and sexual function; however, its influence on plaque size or penile curvature was not conclusive (Hauck et al. 2004a, b). A study on 42 patients by Manikandan et al. (2002) revealed that ESWT is promising and has minimal complications; however, long-term results still needed to be evaluated.

One hundred patients suffering from PD were included in a prospective, randomized, double-blind, placebo-controlled clinical trial by Palmieri et al. (2009). Therapies were performed once a week during four weeks, administering 2000 pulses per session (rate = 4 Hz; EFD = 0.25 mJ/mm^2) with a *Duolith* (Storz Medical AG). Their results were in accordance with articles describing an analgesic effect in approximately 40–100 % of the patients (Lebret et al. 2000; Kiyota et al. 2002; Pryor and Ralph 2002; Poulakis et al. 2006). An advantage of ESWT is that it has no side effects and can be repeated as often as needed. Because of this, it should always be opted for first before surgery (Zimmermann 2013).

6.20 Erectile Dysfunction

The inability to reach and conserve penile erection sufficient for sexual performance is defined as erectile dysfunction (ED). The prevalence of ED in patients between 40 and 70 years is 50 % (Shamloul and Ghanem 2013). In most cases treatment with an oral phosphodiesterase type 5 inhibitor (PDE5I) is effective. The second-line therapy consists in intracavernosal injections with vasodilating agents. Patients who do not respond to PDE5Is and intracavernosal injections are treated with other approaches such as the implantation of a penile prosthesis. ESWT is another option to treat ED (Gruenwald et al. 2013; Lund and Hanna 2013; Lei et al. 2013; Abu-Ghanem et al. 2014; Osornio-Sánchez et al. 2015). An advantage is that it can be repeated in cases where the positive therapeutic effect is short-lasting. The treatment is sometimes called *low-intensity extracorporeal shock wave therapy* (LI-ESWT).

Initial studies reporting that ESWT is tolerable and effective for patients suffering from erectile dysfunction were published by Vardi et al. (2010). The study included ESWT on 20 patients who had previously responded to PDE5Is.

This report was followed by a randomized, double-blind, sham-controlled study that demonstrated a positive effect on the erectile function of men who respond to oral PDE5I therapy (Vardi et al. 2012). Patients discontinued PDE5I during the entire study period and underwent a 4-week PDE5I washout period. Shock waves (EFD = 0.09 mJ/mm^2, rate = 2 Hz) were coupled into the distal, mid and proximal penile shaft, and the left and right crura using a coupling gel for sonography. A total of 300 focused shock waves were delivered at each of the five treatment zones with an *Omnispec ED1000* probe (Medispec Ltd., Yehud, Israel). Only one side of the penile shaft was treated, because the pressure pulses reached both corpora. No local or systemic analgesia was needed. Patients underwent an evaluation using questionnaires and penile hemodynamic testing before and after treatment. A significantly greater increase in the international index of erectile function-erectile function domain (IIEF-EF) was observed in the treated group in comparison with the sham group. No discomfort or adverse effects related to the shock wave treatment were reported. The maximal post-ischemic penile blood flow in the ESWT group was 8.2 ml/min/dl, compared to 0.1 ml/min/dl in the control group.

The efficacy of ESWT for ED patients who respond poorly to PDE5I therapy was studied and published by Gruenwald and colleagues (2012). Patients received two shock wave sessions per week for 3 weeks. Treatments were repeated after a 3-week pause. One month after treatment, an active PDE5I medication was provided during 1 month. Outcome measures and shock wave dose per session were the same as described above. A significant improvement in maximal post-ischemic penile blood flow was observed after treatment. This finding correlated with increases in the IIEF-EF. Nevertheless, the authors concluded that these results have to be confirmed by larger multicenter studies.

Qiu et al. (2013) conducted an in vivo study in a rat model and confirmed that shock waves can partially ameliorate DM-associated ED by examining changes in the erectile tissues. Their report concludes that ESWT promotes regeneration of nNOS-positive nerves, endothelium, and smooth muscle in the penis. In this study, 300 unfocused shock waves at an EFD of 0.1 mJ/mm^2 were administered at a rate of 2 Hz to each animal, three times a week for 2 weeks using a *DermaGold* system (MTS Europe GmbH).

Olsen et al. (2015) performed a prospective, randomized, blinded, placebo-controlled study with 112 men that were unable to have intercourse either with or without medication. The main goal was to determine whether ESWT can be used to treat ED of organic origin. Treatment outcome was evaluated by interview, using the erection hardness scale (EHS) and the IIEF-EF questionnaire. All patients were randomly assigned either to a shock wave or to a placebo group and received five ESWT or sham treatments over 5 weeks. After ESWT 57 % of the patients were able to obtain erection and to have sexual intercourse without the use of medication. In the placebo group 9 % showed similar results. According to the EHS, the shock wave-treated group experienced a significant improvement in their ED; however, no significant improvement could be demonstrated with the use of the IIEF-EF.

The *Renova* linear electromagnetic shock wave source (Direx Systems Corporation), mentioned in Sect. 6.2, was tested by Reisman et al. (2015) in a pilot

study on 58 vasculogenic ED patients and evaluated at baseline and at 1, 3, and 6 months post-ESWT. Among the patients were both responders and non-responders to PDE5Is. Patients received four weekly sessions of 3600 shock waves (EFD = 0.09 mJ/mm^2), i.e., 900 pulses were applied at each of four treatment areas: the penis shaft at the right and the left corpus cavernosum, and the crura at right crus and left crus. The evaluation was done using the IIEF-EF, the Sexual Encounter Profile and the Global Assessment Questions questionnaires. The results suggest that the device is both safe and efficient. A statistically significant increase of the average IIEF-EF from about 15 at baseline to approximately 22 at 6 months post-ESWT was observed. The authors concluded that more than 81 % of the patients had a successful treatment.

Srini et al. (2015) used a focused shock wave probe (*Omnispec ED1000*, Medispec Ltd.) to deliver 300 pressure pulses (EFD = 0.09 mJ/mm^2) at 2 Hz to the distal, mid and proximal penile shaft, and the left and right crura of 95 patients. The device has an electrohydraulic shock wave generator with a small ellipsoidal reflector to focus the shock waves. All the patients underwent a 1 month PDE5I washout period and received 12 sessions of shock waves. The sham therapy group consisted of 40 patients. Outcomes were assessed using the EHS, the IIEF-EF, and the clinical global impression of change (CGIC) scores at 1, 3, 6, 9, and 12 months post-ESWT. The results revealed that the shock wave therapy had a positive long-term clinical effect with improvement in erectile function of men with vasculogenic ED who were prior responders to PDE5I therapy.

ESWT has shown to be safe and efficient and may become a popular therapy for ED, especially for cases not responding to PDE5Is; however, the exact mechanism involved is not fully understood. A hypothesis is that shock waves restore the cavernosal tissue by stimulating tissues that are responsible for erection by releasing the VEGF (a protein that stimulates vasculogenesis and angiogenesis) and the stromal cell-derived factor 1 (a protein that activates leukocytes) (Lei et al. 2013).

6.21 Shock Wave Acupuncture

The so-called *shock wave acupuncture* refers to the use of shock waves or radial pressure waves to stimulate certain receptors to produce effects similar to those achieved with needles. The spots to apply shock wave acupuncture are the same as those of conventional acupuncture with needles. Because of the differences between focused shock waves and radial pressure waves explained in Chap. 3, shock wave acupuncture should be distinguished from *radial pressure wave acupuncture*.

Everke (2007) used a *Masterplus MP 100* ballistic pressure wave source (Storz Medical AG) with a special applicator for acupuncture to treat patients who suffered of *gonarthritis* (osteoarthritis of the knee). Each patient received stimulation at several acupuncture points (between 30 and 60 pressure pulses three times per acupuncture point) every second or third day for up to 12 times. The author reports that therapy outcomes were better than those previously achieved using needle acupuncture.

Acupuncture points directly above bones, the lungs or large blood vessels were avoided. A hypothesis is that ballistic waves are more efficient than needles, because they act on a larger number of pressure receptors and with a higher pressure. In the cases studied, the destruction of cartilage could also have contributed to the superior treatment outcomes. Additionally, it was observed that radial pressure wave acupuncture was more efficient in young patients. According to the results obtained by Everke, radial pressure wave acupuncture is less painful and more successful in the treatment of chronic lumbar pain, *coxarthritis*, i.e., degenerative osteoarthritis of the hip joint, and *gonarthritis* (arthritis of the knee) compared with conventional needle acupuncture (Everke 2005a, b, 2007). A combination of both radial pressure wave acupuncture and needle acupuncture has also been successfully tested (Germann 2011).

6.22 ESWT in Veterinary Medicine

As in human patients, in veterinary medicine the mechanism of ESWT is not fully understood; however, focused shock waves and pressure pulses induce analgesic effects in dogs, improving their vitality and quality of life. Common indications for ESWT in canine orthopedics are fracture non-union, hip dysplasia, knee and elbow arthritis, as well as tendinopathies. Shock or radial waves should not be applied over implants, on animals that had a recent surgery, skeletal immaturity, or coagulation disorders. Other contraindications are tumor patients, acute inflammations, acute episodes of joint disease, neoplasia, and infection. Combining ESWT with other therapies, such as massage and exercises is recommended. To assure good coupling of the pressure waves, the target zone must be shaved and ultrasound coupling gel has to be applied. Sedation or light anesthesia may be necessary, specially when focused shock waves are used. Petechia, swelling, and short-term aggravation of the problem are possible side effects.

ESWT is a routine to treat horses. Shock wave sources designed for these animals have been on the market for many years. Treatment of stress fractures, osteoarthritis, and injuries in tendons and ligaments are common (McClure et al. 2004a, b; Dahlberg et al. 2005; Kersh et al. 2006). Indications for equine ESWT include navicular syndrome, flexor tendons, coffin joint, coffin bone, and common tendon sheet insertion. The thoracic muscles, sacroiliac joints, croup muscles, and upper neck muscles are also treated with shock waves and radial pressure waves. Nevertheless, reported clinical outcomes have not been always consistent. As occurs with human patients, the reason for this might be the use of different pressure wave sources and treatment protocols. For instance, Brown and colleagues (2005) could not achieve improvement of equine lameness with a ballistic pressure wave source, while Dahlberg et al. (2006) reported a statistically significant pain decrease using an electrohydraulic shock wave generator. Because of the difference in the acoustic field emitted by non-shock wave generating ballistic sources and electrohydraulic shock wave emitters, discrepancies in treatment outcomes should not be a surprise.

Chapter 7
Novel Uses and Potential Applications

7.1 Introduction

Shock wave research has extended enormously during the last two decades. This chapter can be a reference for the experienced researcher; however, it was mainly written to encourage students and scientists from other areas to enroll in novel topics of shock wave research. Promising methodologies and developments of potential medical and biomedical applications are described. Nevertheless, it should not be considered as a review of worldwide shock wave research.

In the first part of this chapter, some experimental studies to develop novel uses of shock waves such as drug delivery, needleless injection, thrombus ablation, enhancement of bone fusion to treat skull bone defects, and pain release in neuralgia are described. Several studies dealing with gene transfection, i.e., the delivery of deoxyribonucleic acid (DNA) into cells, as well as with the enhancement of the cytotoxic effect of drugs, to treat oncological diseases using shock waves are explained in Sect. 7.4. Transformation of bacteria and filamentous fungi is a continuous challenge in biotechnology, agriculture and the food, chemical and pharmaceutical industry. More efficient methodologies for delivering exogenous nucleic acid to bacteria and fungi are still needed. As will be described in Sects. 7.5 and 7.6, a promising approach is the use of underwater shock waves. The bactericidal action of shock waves, discussed in Sect. 7.7, has been studied by many groups for a variety of scenarios and potential applications. In the near future, extracorporeal shock waves may also be beneficial in dentistry. Potential applications such as bone regeneration and the elimination of bacterial biofilm are discussed in the final section of this chapter.

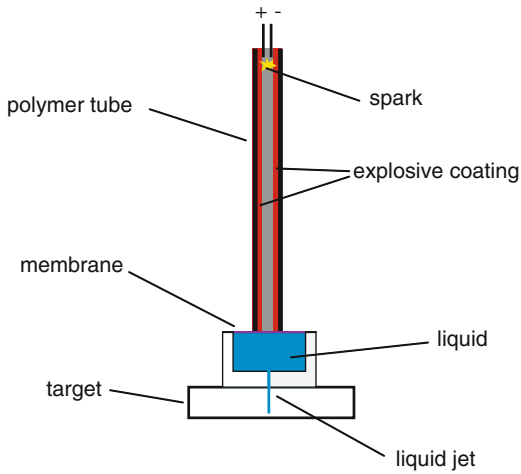


Fig. 7.1 Schematic of a needleless device to deliver drugs or vaccines into biological systems, consisting of an ignition system, a small polymer tube coated with explosive material, a metal membrane, and a drug-holding chamber containing the liquid to be injected. Adapted from Jagadeesh et al. (2011)

7.2 Needleless Injection and Small Shock Tubes

A needleless device to deliver drugs or vaccines into biological systems was designed by Jagadeesh et al. (2011). It consists of a small polymer tube, coated with explosive material on the inner wall (Fig. 7.1). When the explosive is ignited, a shock wave propagates along the tube and a thin metallic membrane at its end transfers the impulse to the liquid contained in a drug-holding chamber at the other side of the membrane. The sudden movement of the membrane compresses the liquid, which is ejected as a liquid jet through a small nozzle into the target. Another group reported the use of an infrared nanosecond laser pulse to produce shock waves for the needleless injection of small amounts of liquid drugs (Han et al. 2012). In this needless syringe, a laser is focused on distilled water contained within a transparent chamber, producing a plasma bubble by optical breakdown. The sudden expansion of the bubble compresses the surrounding liquid which flows radially outward, generating a spherical shock wave thus deforming a thin silicon membrane that acts as a piston and pushes the drug inside a small nozzle. The drug is expelled out of the nozzle as a high-speed microjet. A second microjet is caused by a second shock wave produced because of bubble collapse.

Recently, Battula et al. (2016) reported the design of a needle-free miniature shock wave driven device to inject liquid drugs into human skin. The system is minimally invasive and releases vaccines or drugs to the depth of dermal blood vessels. In their report, the authors analyze the velocity of the generated jet and the pressure exerted by the jet on the target. Initial trials were performed by delivering the liquid jet into samples of human skin and gelatin slabs. The main goal of the project is to develop a safe and cost-effective needle-free injector. Systems as described in this section will become popular in the near future.

A miniature, hand-operated, pressure-driven, shock tube named *Reddy Tube*, to be used in biomedical applications, was developed by KPJ Reddy (Reddy and Sharath 2013). Similar to large shock tubes, the device consists of a driver section and a driven section, separated by a diaphragm. Compressed gas in the driver section

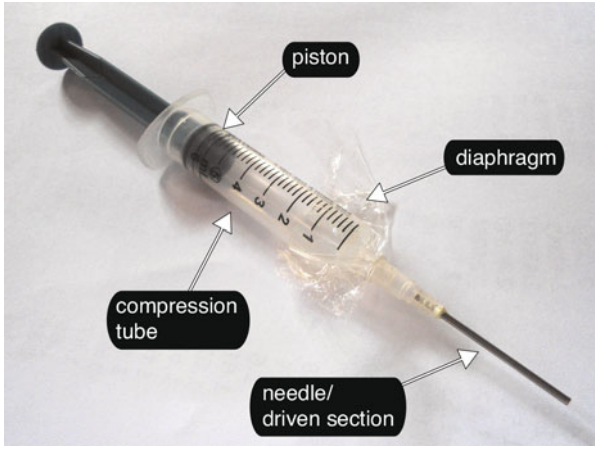


Fig. 7.2 Photograph of a plastic syringe-based Reddy tube. (Courtesy of KPJ Reddy)

ruptures the diaphragm generating a shock wave which travels through the driven section. In the initial experiments a medical syringe was used to compress air by the inward motion of the plunger. The hypodermic needle acted as the driven section of the shock tube. Both elements were separated by a thin layer of plastic or cellophane (Fig. 7.2). As the plunger is pressed towards the diaphragm, the air in the syringe is compressed, until the diaphragm ruptures and forms a shock wave within the needle. With this simple device, Mach numbers exceeding 1.5 could be recorded by simple hand operation. The device was optimized and the flow emerging from its open end was visualized using a high-speed camera and schlieren imaging. The images revealed a diffracting spherical shock wave followed by a strong vortex ring emitted from the miniature shock tube. This novel hand driven shock tube has a variety of applications. A modified version of the device, coupled to an artificial insemination gun, has been successfully tested to deliver bull semen to increase the chances of artificial conception in farm animals. Another application of the Reddy Tube, which was tested in vitro, is brain tumor softening. The killing of certain species of beetle that affect coffee plantations has been proposed as another possible beneficial use of the shock tube. Shock waves, delivered through the exit hole of tunnels bored by the insects, killed them instantaneously.

To carry out measurements of the flow fields inside the driven tube, a scaled-up stainless steel version of the shock tube (29 mm in diameter) was developed (Reddy and Sharath 2013; Kumar and Reddy 2016). It consists of a 400-mm long driver section and a 600-mm long driven tube, separated by a diaphragm of tracing paper or aluminum foil (Fig. 7.3). A plunger with a rubber head similar to that of a large veterinary syringe is forced along the driver section to create the pressure required to burst the diaphragm. Mach numbers in the range of 1.2–2.0 can be easily generated. This hand-operated shock tube can be further extended into a hypersonic shock tunnel, capable of generating a freestream flow of Mach 6.5 in the test section. The device is a valuable tool in high-speed aerodynamics, being a substitute to more expensive and larger systems. The Reddy tube itself finds far reaching applications in several fields, including chemical kinetics. Numerical simulations of shocks in a single diaphragm shock tube were compared with experimental measurements

Fig. 7.3 Photograph of a hand driven shock tube used as a teaching tool, showing (*1*) the driver section, (*2*) the diaphragm station, (*3*) the driven section, (*4*) the convergent–divergent nozzle, (*5*) the test section, and (*6*) the dump tank. (Courtesy of KPJ Reddy)

recorded using the Reddy Tube by Surana and colleagues (2014). The novel shock tube has also been used to study the neuropathological changes occurring in the rat brain when exposed to different blast peak pressures (Bhat et al. 2014).

7.3 Ablation and Neurosurgery

Cerebral embolism occurs when blood clots obstruct cerebral arteries. Thrombus ablation using shock waves has been tested in vitro to explore a possible method for noninvasive mechanical thrombolysis (Rosenschein et al. 1992). Thrombi inserted into ligated excised human femoral artery segments were exposed to shock waves at the focus of a shock wave source. Significant ablation was achieved. The authors reported that the principal ablation mechanism seemed to be acoustic cavitation. No damage to the arterial segments was observed. As mentioned in Chap. 2, the first non-invasive shock wave thrombolysis treatment (NISWT) was done in 1998. A total of 800 shock waves having an energy flux density (EFD) of 0.04 mJ/mm^2 were focused on a stable, echogenic thrombus at the femoral vein. Flow, which was not observed before treatment, was seen by color duplex and Doppler ultrasound immediately after NISWT, and at one, two, and three months follow-up. No side effects were observed. After demonstrating the feasibility of NISWT, Belcaro et al. (1999) evaluated the technique on selected patients having echogenic thrombi. A *Minilith SL1* shock wave source (Storz Medical AG, Tägerwilen, Switzerland) was modified for this specific

application. Shock waves were coupled to the target area through the silicon water cushion of the shock wave source. The pressure (p^+) at the focal spot of the *Minilith SL1* can be varied between 6 and 70 MPa in eight steps (EFD 0.03–0.5 mJ/mm^2). Four sessions (one per week) of 1000 shock waves were performed at intensity level 2 on each patient. Thrombolysis was achieved in selected cases and was still present after four months. Echolucent "holes" and flow were observed after therapy, demonstrating that NISWT induces a fast recanalization of femoral thrombi. No side effects were observed after treatment or within a four-month follow-up.

Shock waves are also potential tools in neurosurgery. Tominaga and colleagues (2006) developed and tested a compact shock generator to be used in microsurgery. In their device, laser beam irradiation in a liquid-filled catheter produces water vapor bubbles and shock waves. Consequently, liquid microjets are emitted from a nozzle at the exit of the catheter.

Hasebe et al. (2015) designed a shock wave catheter ablation (SWCA) system to destroy abnormal electrical pathways that contribute to cardiac arrhythmia and performed the first feasibility experiments in pigs in vivo. So far, radio-frequency has been used to selectively necrotize tissue; however, the limited depth of treatment due to the thermal conductivity of the tissue and the risk of thrombus formation are considered as weaknesses of this technique. The novel device (Fig. 7.4) consists of a miniature water-filled semi-ellipsoidal reflector attached to a catheter tip with a 14-French diameter (approximately 4.7 mm). A shock wave is generated at the inner focus (*F1*) of the reflector by a Q-switched Holium: yttrium-aluminum-garnet

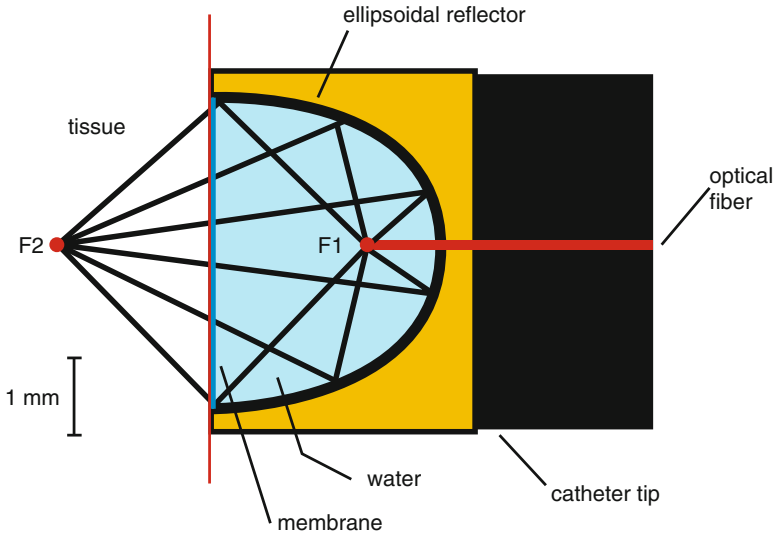


Fig. 7.4 Sketch of a miniature shock wave generator, attached to a 14-Fr catheter tip. The shock waves produced by a Holium-YAG laser at the first focus (*F1*) of the reflector are focused towards *F2*. A possible application is the destruction of abnormal electrical pathways that contribute to cardiac arrhythmia. Adapted from Hasebe et al. (2015)

(YAG) laser beam, sent through a quartz optical fiber. Analogous to electrohydraulic shock wave generators (Sect. 5.2.1), the shock wave produced at *F1* is reflected off the reflector and focused onto the outer focus *F2*. Application of 180 shock waves ($p^+ = 40$ MPa; rate = 1 Hz) with the SWCA system caused persistent myocardial lesions and sustained atrioventricular conduction disturbances with an endocardial approach. Atrioventricular conduction refers to the conduction of electrical impulses through the part which controls the heart rate. No fatal adverse effects occurred. At p^+ values above 40 MPa, injury was also noted at the pre-focal zone. Peak-positive pressures under 30 MPa caused no tissue injuries. It seems that the miniature shock wave generator causes tissue injury through acoustic cavitation and shear forces. Even if the system still needs improvements, in the future, this non-thermal technique could help to reduce the risk of thrombogenesis.

7.4 Cell Transfection and Oncology

Cell transfection, defined as the introduction of genetic material into cells to reprogram cellular function, opening the possibility to treat inherited or acquired disorders, such as inborn errors of metabolism, atherosclerosis and cancer, is emerging as a promising tool (Kaufmann et al. 2013). The strategy for gene therapy is either to identify a mutant gene causing a disease, and providing the defective cells with the correct DNA, or to transfer a genetic construction to silence a crucial process in the pathogenesis of a disease. Transferred DNA can inhibit or enhance certain cell functions, introduce new functions into a cell or replace defective genes. Well-known features of DNA are that it can produce copies of itself and that it contains the genetic information for the development of living organisms coded as the sequence of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). The bases pair up (A with T and C with G) to form the so-called *base pairs* (bp), which are attached to a sugar moiety and linked through phosphate bonds to form the popular double helix. However, a limiting condition of gene therapy is the fact that DNA is a large and charged molecule that cannot diffuse through the cell membrane. Bacteria have the so-called *plasmids*, i.e., small DNA molecules that exist separate from the chromosomal DNA, which are crucial in genetic therapy. They usually carry only a few genes and are important for microorganism survival under specific conditions by providing adaptability, for instance, by determining the production of proteins to make a bacterium resistant to a specific antibiotic (Sect. 7.5). Plasmids consist of polymers of nucleotides forming two helical chains coiled around the same axis, and contain additional genetic information. Their size varies between one and more than 100 kilobase pairs (kbp).

In many cases, the genetic fragment is expressed, but not included in the chromosomes. This is referred to as *transient transfection*. The incorporation of the transferred gene into the genome is called *stable transfection*. Gene delivery can further be divided into *viral* and *non-viral*. Non-viral strategies include chemical and physical methods. So far, most vectors used in clinical tests are *adenoviral*. They are

constructed by introducing a therapeutic gene and altering the viral genome so that the virus is incapable of replication and therefore infection. Viral vectors are very efficient for in vivo and in vitro gene delivery; however, the method involves biological risks, such as carcinogenesis, uncontrolled host immune response, and difficulty of vector production. Furthermore, the use of viral vectors is expensive and requires strict safety regulations. Because of this, a major challenge is to deliver genes into cells of solid organs at specific genome areas, by means of non-viral strategies (Neuman et al. 1982; Cemazar et al. 2002). Electroporation (Lohr et al. 2001), lipofection (Karara et al. 2002), micro-injection (Kaneda 2001), single cell optical transfection (Stevenson et al. 2010), gene transfection by laser-induced breakdown of optically trapped nanoparticles (Arita et al. 2011), as well as micro- and nano-particle bombardment using gene guns (Yang et al. 1990; Uchida et al. 2009; O'Brien and Lummis 2011) have been the object of considerable research; however, in vivo application of these methods is either limited or impossible.

Several authors have reported that the creation of transient holes in the cell membrane using ultrasound or shock waves, a process called *sonoporation*, is possible as a tool to internalize DNA, short interfering ribonucleic acid (siRNA), antibodies, and chemotherapeutic drugs both in vitro and in vivo (Laudone et al. 1989; Gambihler et al. 1990, 1994; Debus et al. 1991; Steinbach et al. 1992; Cornel et al. 1994; Prat et al. 1994; Delius et al. 1995b; Mastikhin et al. 1995, 2010; Prat and Arefiev 1995; Bao et al. 1997, 1998; Lauer et al. 1997; Huber et al. 1999b; Koch et al. 2000; Kodama et al. 2000; Miller 2000; Tschoep et al. 2001; Miller and Song 2002, 2003; Miller et al. 2002; Song et al. 2002; Michel et al. 2003, 2004; Schaaf et al. 2003; Armenta et al. 2006; Schlicher et al. 2006; Bekeredjian et al. 2007; Reslan et al. 2010; Liu et al. 2012a; Lo et al. 2014; Millán-Chiu et al. 2014; Chettab et al. 2015; Mestas et al. 2015; Carrasco et al. 2016; Lafond et al. 2016). Some cells survive and repair the damage caused to their membrane, allowing large molecules to become part of the cell machinery. This can be demonstrated by the expression of reporter genes contained in plasmids or by the internalization of special dyes. An interesting advantage of acoustic waves is that they can be focused within the body so that non-viral in vivo transfection could be achieved at specific sites.

A few years after the introduction of extracorporeal shock wave lithotripsy (SWL) it was hypothesized that targeting organs with shock waves after local DNA application or delivery via the circulation is feasible to delay tumor growth. In vitro and in vivo research followed since then; however, with limited success, because the technique was conceived in a time when the mechanisms of shock wave-interaction with cells and living tissue were poorly understood. Delayed tumor growth was achieved in animal models; however, complete remissions were rare (Oosterhof et al. 1991). Nevertheless, encouraging results appeared by combining biological response modifiers and cytotoxic drugs with shock wave therapy in vivo, a technique called extracorporeal shock wave chemotherapy (ESWC). Cavitation and free radical production are believed to be responsible for the observed effects. Nonetheless, there is still more research needed before shock wave therapy of inherited or acquired disorders can be introduced into clinical practice. As will be seen in this section, different strategies to treat cancer with shock waves have been followed: tumor growth reduction by

combining shock waves with anticancer drugs, tissue necrosis after shock wave exposure of the tumor, and cell transfection to reprogram cellular function.

According to the in vitro studies published many years ago by Russo et al. (1986), exposure of rat prostatic carcinoma and human melanoma cells to shock waves as used in SWL resulted in a reduction in cell viability and a decrease in the number of colonies formed in a clonogenic assay. Furthermore, the authors reported that when shock wave-treated rat prostatic carcinoma cells were injected into healthy rats, or when tumor-bearing animals were treated with shock waves focused on the tumor, a delay in tumor growth was seen, demonstrating that shock waves cause death of tumor cells both in vitro and in vivo. The same research group observed cell fragmentation after shock wave exposure of cell suspensions. They also reported that after shock wave treatment of tumor cells, mitochondria were swollen and contained distorted cristae (folds of the inner mitochondrial membrane) (Russo et al. 1987). In vivo shock wave treatment of tumor nodules did not cause histopathologic or ultrastructural effects that could be distinguished from spontaneous cell death.

The in vitro cytotoxic effect of different numbers of shock waves on renal cell carcinoma cells was compared to the effect on normal human embryonic kidney cells by Randazzo et al. (1988). Cell viability, cell growth, cell attachment, and electron microscopy evidence of ultrastructural damage were analyzed. Cells exposed to 2000 shock waves, generated with an *HM3* lithotripter (Dornier MedTech GmbH, Wessling, Germany) at a discharge voltage of 18 kV and a rate of 100 shock waves per minute, showed a significant decrease in renal cell carcinoma viability. A significant difference in damage between the two types of cells was observed after treatment with 2000 shock waves. Viable in vitro treated cells had an identical growth to the control at 12 days after exposure to shock waves, regardless of the shock wave dose. Additionally, in vivo-induced bladder tumors were transplanted into the right hind legs of mice and exposed to shock waves on the same lithotripter. The anesthetized animals were placed in a special protective tube that had a hole on the side to allow the right hind leg to exit so that the tumor could be placed at the *F2* focus of the shock wave generator. Significant tumor growth reduction was observed after exposure to 1400 shock waves (18 kV) at day 12 post-transplant. Combining the same amount of shock waves with the anticancer drug cisplatin did not inhibit tumor growth; however, the chemotherapeutic agent doxorubicin and 1400 shock waves resulted in a significant synergistic tumor reduction.

Wilmer et al. (1989) showed that 500 underwater shock waves generated by an electrohydraulic *XL1* experimental lithotripter (Dornier MedTech GmbH) at a voltage of 25 kV (capacitance 80 nF) induced an increase in the susceptibility of mouse leukemia cells to the chemotherapy drug cisplatin. After analyzing the effects of shock waves on clonogenic growth and on drug sensitivity of human tumor cells in vitro, Berens et al. (1989) confirmed that shock waves may have utility as a cancer treatment modality either alone or in combination with cytotoxic agents. Three different chemotherapeutic agents (cisplatin, doxorubicin, and 4-hydroperoxycyclophosphamide) were each more effective in blocking cell growth after shock wave treatment ($p^+ \approx 100$ MPa; $p^- \approx -10$ MPa) with an *HM3*

(Dornier MedTech GmbH) lithotripter operated at a fixed discharge voltage of 18 kV and a rate of 100 shock waves per minute.

According to a study published by Bräuner and coworkers (1989), mouse leukemia cells, human cervical cancer cells (HeLa), and multicellular tumor spheroids exposed to 500 shock waves in an *XL1* (Dornier MedTech GmbH) showed significant cellular damage. Interestingly, spheroids immobilized in gelatin and exposed to the same shock wave dose were not different from control cultures. A plausible reason for this finding is that cells in gelatin were subjected to less acoustic cavitation (Sect. 4.7). Similar findings were published by Brümmer and coworkers (1989).

A classical publication by Laudone et al. (1989) describes several factors that influence the results and interpretation of experiments which investigate the cytotoxic potential of shock waves. The type of test vial, the presence of a fluid–air interface inside the vial, as well as the differences between in vitro and in vivo shock wave exposure of cells, and the need for appropriate negative controls for in vivo experiments were considered. At the end of the 1980s and beginning of the 1990s, many authors reported that the cytotoxic effect of shock waves is dependent on the cell type, the volume of the tumor, and the shock wave dose, i.e., the number and energy of the shock waves (Oosterhof et al. 1989, 1990a, b).

The effects of shock waves generated with a *Lithostar* (Siemens Healthcare GmbH, Erlangen, Germany) lithotripter (Sect. 5.3.1) alone or combined with biological response modifiers (BRM) or a chemotherapy agent (Adriamycin), on the growth of human cancer xenografts were studied in nude mice. A delay in tumor growth after four sessions of 800 shock waves (on days 0, 2, 4, and 6), compared with tumor growth following a single shock wave treatment, was observed. Several days after therapy, the tumors regained their original growth rate. The combination of four shock wave sessions and a single Adriamycin administration suppressed the growth of the tumors for a longer period, and the combination of interferon alpha, tumor necrosis factor alpha (subcutaneously injected around the tumor), and shock waves resulted in complete cessation of tumor growth. A few years later, Oosterhof et al. (1996) investigated the hypothesis that exposure of a tumor to shock waves could lead to metastases. A highly metastatic rat prostate cancer line was implanted in the hind limb of rats. Tumors of about 175–225 mm^3 were exposed to 6000 shock waves (EFD = 0.47 mJ/mm^2), generated at a rate of 2 Hz with an experimental *Lithostar Plus* (Siemens Healthcare GmbH) shock wave source. During treatment, the anesthetized rats were kept in a plastic tube placed in a water bath containing degassed water. Metastases were seen in 82 % of the shock wave-treated animals and only in 25 % of the sham treated animals.

The in vitro antitumor effect of shock waves was confirmed by Kohri et al. (1990) after exposure of bladder tumor cells, chronic bone-marrow leukemic cells, and African green-turtle normal kidney cells, to underwater shock waves at the *F2* focus of an *HM3* lithotripter (Dornier MedTech GmbH) operated at a discharge voltage of 18 kV and a rate of 100 shock waves per minute. A reduction in cell viability was determined by ^{3}H-thymidine incorporation assay and flow cytometry. The ^{3}H-thymidine incorporation test is a methodology wherein radioactive ^{3}H-thymidine is incorporated into strands of chromosomal DNA during mitotic cell division.

The amount of cell division that occurs in response to shock wave action is determined by measuring the radioactivity in DNA recovered from the cells. The authors found that chronic bone-marrow leukemic cells were the most sensitive while African green-turtle normal kidney cells were the most resistant to shock waves. Destruction of microvilli over the cell surface and swollen mitochondria in leukemic cells and bladder tumor cells were observed on electron microscopy.

To study the potential of shock waves to control cancer, Lee et al. (1990) exposed subcutaneous murine bladder cancer in mice to shock waves alone or in combination with cisplatin. Shock waves were generated at a rate of 100 shock waves per minute with an *HM3* lithotripter (Dornier MedTech GmbH). The authors designed a mice holder consisting of five inner holders (centrifuge tubes with a hole for the right hind limb) and a polypropylene jar as an outer shell, to expose the tumors of five anesthetized mice simultaneously. The outer shell was positioned in the water tub of the lithotripter and partially filled with water so that the tumor sites were approximately 10 mm underwater. Before initiating the treatment, the five right hind limbs were moved close together to focus the shock waves on the five tumor sites. Tumors were exposed to various numbers of shock waves (250 to 1500), generated at a voltage between 18 and 22 kV. Mice with three day or seven day tumors were exposed to shock waves with or without cisplatin. The results demonstrated that up to 1500 shock waves alone showed no influence on tumor growth; however, the shock wave treatment significantly enhanced the antitumor effect of cisplatin. A hypothesis is that shock wave-induced free radicals had a chemo-sensitization effect. In a similar study, Holmes et al. (1990) reported the outcomes of exposing rat prostate tumors grown on the right hind limb of male Copenhagen rats to 2000 shock waves alone or in combination with cisplatin. To initiate the tumors, cultured cells were injected with phosphate-buffered saline solution (PBS) subcutaneously in the mentioned spot. Shock waves, generated at 20 kV with an experimental *XL1* shock wave source (Dornier MedTech GmbH), were administered at a rate of 1 Hz to the tumors about seven days after inoculation. Clonogenic cell survival 24 h after treatment, tumor growth delay, and the number of lung metastases were determined. The survival of clonogenic cells was reduced 38 % by shock wave treatment and tumor growth was delayed by 1.5 days. The shock wave treatment increased the effectiveness of chemotherapy and did not promote dissemination of tumor cells. Shock waves combined with cisplatin delayed the time taken for the tumor to reach one cubic centimeter by 13 days in comparison with untreated controls; however, the combined therapy increased the mortality from 9 % with cisplatin alone to 29 %.

Initial reports by Hoshi et al. (1991) on the effects of single sessions of 2000–8000 shock waves on implanted urinary bladder cancer in rabbits revealed only focal necrosis of the tumor; however, wider and deeper tumor necrosis was detected after exposing the tumors to multiple shock wave sessions. Decreased tumor growth in comparison with that of the controls was observed after 8- to 10-day serial shock wave exposure (6000–8000 shock waves). The shock wave therapy did not promote lung metastases. According to the results, shock waves induced vascular injury in the tumors, which appeared to be the primary cause for tumor necrosis.

As well as in other studies mentioned in this section (Bao et al. 1998; Song et al. 2002; Michel et al. 2003), Prat and colleagues (1991) enhanced shock wave-induced cavitation by administration of gas microbubbles. Their aim was to observe whether this method could hinder cancer cell proliferation. In the first part of the study, bubbles from a mixture of air and gelatin were added to suspensions containing human colon carcinoma cells (HT-29). In the second part, bubbles from a carbonated NaCl solution were administered to tumors (peritoneal nodules from a rat colon carcinomatosis) in vitro. HT-29 cells in suspension were exposed to 50, 250, or 1000 shock waves alone or in combination with bubbles, inside polypropylene assay tubes. The tumor nodules were placed in the same type of tubes with treatment medium and received either 50, 100, 250, 500, or 1000 shock waves only or shock waves with bubbles in the suspension. An electrohydraulic lithotripter (*Sonolith 3000*, Technomed Medical Systems, Vaulx-en-Velin, France) was used to produce shock waves at a rate of 2 Hz. The results of the first part showed that as the number of shock waves increased, trypan blue-negative cells decreased. Trypan blue is a dye used to determine the number of viable cells in a cell suspension. Live cells possess intact membranes that exclude the dye from penetrating the cell, whereas dead cells do not. Exposure to cell suspensions with bubbles resulted in an increased mortality as compared to suspensions without bubbles. The highest shock wave number applied to vials containing bubbles induced a complete inhibition of cell growth, with cytoplasmic vacuolae, ruptured membranes, and abnormal nuclear shape and chromatin (macromolecules found in cells, consisting of protein, DNA, and RNA). Exponential and confluent cells exhibited a similar mortality and growth. The histopathological analysis of tumors exposed to shock waves with bubbles showed erosion and hemorrhage, disorganized structure, cytoplasmic vacuolae, and pyknotic nuclei, i.e., condensation of chromatin in the nucleus. The authors concluded that shock wave microbubble-enhanced acoustic cavitation can achieve bioeffects which are relevant to cancer therapy.

A systematic examination of shock wave-induced intracellular damage to human prostate carcinoma cells was performed by Steinbach et al. (1992) with a *Lithostar Plus* (Siemens Healthcare GmbH) electromagnetic shock wave source coupled to a water bath. In the first part of their study, cell suspensions were exposed to shock waves (EFD between 0.12 and 0.6 mJ/mm^2) inside polypropylene tubes. A suspension–air interface was left in half of the samples. The remaining tubes were completely filled with cell suspension at the same concentration. The number of shock waves was varied between 100 and 400. Multicellular tumor spheroids and cells grown on microcarriers were exposed to 200 shock waves in the second part of the experiment. To avoid motion of the specimen, the spheroids were covered with an agarose-filled plastic stamp. Four EFD values were tested (0.12, 0.21, 0.33, and 0.5 mJ/mm^2) at a shock wave rate of 1 Hz. As expected, a significant increase in cell loss was found in tubes containing air. The reason for this is that reflection of the shock wave at the cell suspension–air interface increases acoustic cavitation and changes the forces on the cells (Sects. 4.3 and 4.7). It was also observed that a tenfold cell concentration did not influence cell loss. This indicates that intracellular collisions do not contribute significantly to cell damage. Laser scanning microscopy

following fluorescence staining was used to study the intracellular damage of intact spheroids. Interestingly, depending on the EFD, different sensitivities of individual cell components were observed. The most sensitive cell component was the plasma membrane. The next sensitive components were the intermediate filaments, followed by the microtubules. Effects on mitochondria appeared at an EFD of approximately 0.33 mJ/mm^2. The nucleus was the least sensitive component to shock wave treatment. An EFD of 0.5 mJ/mm^2 was needed to induce significant morphological changes.

An experiment to study the potential efficiency of ESWC on normal and malignant human, rat, mouse, and chicken cells suspended in PBS was published by Brümmer et al. (1992). The authors concluded that the acute cytotoxic effect, measured by flow cytometry, was a function of the shock wave dose. The shock wave-treated cells differed in their median lethal dose (dose required to kill half the cells of a sample). No general difference in sensitivity to shock waves was observed between normal and tumor cells. Furthermore, Gambihler and Delius (1992) studied the effect of shock wave exposure of mouse leukemia cells during incubation with five different cytotoxic drugs (cisplatin, doxorubicin, daunorubicin, THP-doxorubicin, or aclacinomycin). Cisplatin and doxorubicin were selected because they are widely used in cancer therapy. The other three drugs were chosen because they cover a wide range of lipophilicity (ability to dissolve in lipids, fats, and oils). An *XL1* electrohydraulic shock wave generator (Dornier MedTech GmbH) was used to expose the cells to shock waves generated at different voltages (capacitance 80 nF). At the minimum (20 kV) and maximum (26 kV) voltage, the waveform produced by the *XL1* has a peak-positive pressure of approximately 82 and 92 MPa, respectively. Cell suspensions were exposed to shock waves at a rate of approximately 1.7 Hz inside polypropylene vials positioned so that the focus (*F2*) of the shock wave source was located 10 mm above their bottom. The test tank was filled with degassed water at approximately 36 °C. Cell viability was determined by trypan blue exclusion. Dose–response curves were obtained for each drug with a number of incubation times, with or without exposure to 500 shock waves. Different drug concentrations were tested. A dose–response curve with 500 shock waves generated at different voltages (15, 20, and 25 kV) with or without simultaneous incubation with cisplatin was also obtained. Dose enhancement ratios were determined for each drug. The results revealed that these ratios increased for the drugs with decreasing cytotoxicity. Compared with the other drugs, the efficiency of cisplatin was most significantly enhanced by the shock wave treatment. In all cases, the desired effect improved as the shock wave energy was increased. The authors hypothesized that the observed phenomena was due to shock wave-induced cellular membrane permeability.

An in vitro study on the permeabilization of mouse leukemia cell membranes using shock waves, generated with the same experimental device at a voltage of 25 kV and a rate of 1 Hz, was published two years later by the same research group (Gambihler et al. 1994). Samples were exposed to 250 shock waves, either before or during incubation with fluorescein-labeled dextran (FD). Control samples were incubated with FD alone. Permeabilization was detected by evaluating the accumulation

of FD with a relative molecular mass (ratio of the average mass per molecule of an isotopic composition to one-twelfth of the mass of an atom of carbon-12) between 3.9×10^3 and 2×10^6. A dose- and time-dependent increase in cellular fluorescence (determined by flow cytometry) with a vesicular distribution pattern in the cells consistent with endocytotic uptake was caused by incubation with labeled dextran alone. Similar fluorescence intensities were obtained when comparing shock wave exposure prior to incubation with labeled dextran, to incubation with labeled dextran alone. If cells were exposed to shock waves in the presence of labeled dextran, the cellular fluorescence was further increased. This demonstrated additional internalization of the probe. The higher shock wave-induced cellular fluorescence was found to be located in the cytosol of the cells. Permeabilized cells were viable and proliferated. Degradation of the dextrans from exposure to shock waves was not observed. The authors concluded that in vitro shock wave-induced permeabilization of mouse leukemia cell membranes allows loading of dextrans with a relative molecular mass of up to 2×10^6.

Another interesting article, published by Gamarra and colleagues (1993a), reported successful in vivo shock wave therapy of amelanotic melanomas (a type of skin cancer) in the dorsal skin of golden hamsters. An *XL1* experimental electrohydraulic shock wave generator (Dornier MedTech GmbH) was used to apply shock waves (discharge voltage 15 kV, capacitance 80 nF, and shock wave rate 2.3 Hz) to the center and to 5 sites on the margin of the tumors, seven days after implantation. Anesthetized hamsters were placed in a Plexiglas tube that was closed at its posterior end. Styrofoam inside the tube protected the animals from shock wave passage. The tube with the hamster was positioned inside the water tank of the *XL1*, and the tumor-bearing skin was exposed to shock waves through a slit in the tube. An untreated group and a group of animals undergoing surgical resection served as controls. A complete reduction of the tumor was achieved in more than 90 % of the shock wave-treated hamsters and in the same percentage of surgically treated hamsters. The frequency of metastasis was the same in both groups. All tumors in the non-treated control group continued to grow. The same research group also studied the extent and duration of perfusion changes in tumors during the first hours after a single shock wave treatment (Gamarra et al. 1993b). Golden hamsters bearing two amelanotic melanomas in the dorsal skin served as an animal model. Shock wave therapy was applied using the same *XL1* device mentioned before. One of the tumors was randomly chosen, positioned at the *F2* focus of the shock wave source and exposed to 200 shock waves generated at a discharge voltage of 15 kV (capacitance 80 nF) at a shock wave rate of 2.3 Hz. The second tumor was not exposed to shock waves and served as an intraindividual control. Mean blood flow was determined using autoradiography with iodo [^{14}C]antipyrine. A temporary reduction of tumor perfusion after therapy was observed as a consequence of shock wave-induced damage to the tumor circulation.

Further studies on the combined use of shock waves and drugs were reported by Wörle et al. in 1994. The authors analyzed the effects of shock waves in combination with three cytostatic drugs (cisplatin, mitomycin, and actinomycin) and the two cytokines (small proteins released by cells that affect other cells) interferon alpha

and tumor necrosis factor alpha, on several bladder cancer cell lines. Dose enhancement ratios were obtained for different sequences and doses of shock waves generated with a *Lithostar Plus*-based experimental electromagnetic lithotripter (Siemens Healthcare GmbH). Vials containing cell suspensions were positioned in the focus and exposed to 200 or 1000 shock waves with an EFD of 0.33 mJ/mm^2, or to 200 shock waves with an EFD of 0.6 mJ/mm^2. It was observed that shock waves could render certain cell lines more susceptible to subsequent cytostatic drugs. The antiproliferative effect was most pronounced after concomitant shock wave and drug treatment. Shock waves also caused damage to cell organelles and alterations in cellular metabolism. A few years later, Kambe et al. (1997) published results obtained after examining the influence of shock waves in combination with three anticancer agents (bleomycin, cisplatin, and 5-fluorouracil) on various human cancer cells. According to their tests, chemotherapeutic enhancement was proportional to the shock wave energy used. The improvement in terms of the tumor growth curve could be demonstrated in all cell lines only with bleomycin.

To investigate the mechanisms for DNA damage induced by a spark-gap shock wave source, Miller et al. (1996) exposed Chinese hamster ovary cells suspended in PBS inside small test vials to shock waves at the *F2* focus of a shock wave lithotripter. The temperature in the water bath was maintained at 37 °C. Cell viability was verified by trypan blue exclusion, and DNA strand breaks were evaluated by gel electrophoresis. About half of the cells were destroyed and significant DNA damage in surviving cells was found after 500 discharges. During in vitro shock wave exposure with an open-bath electrohydraulic shock wave generator, the cells located in the vicinity of *F2* receive ultraviolet and visible radiation coming from the high-voltage electric discharge at *F1* (Sect. 5.2.1). By blocking the radiation coming from *F1* and only allowing shock wave passage through the test vials, the authors observed that DNA damage, but not cell lysis, disappeared. The observed DNA damage seemed to result from exposure of cells to the ultraviolet light emissions of the spark-gap discharge, rather than to the action of the shock waves and their effects (cavitation and secondary shock wave emission). Nevertheless, as explained in the next section, other authors (Campos-Guillén et al. 2012) exposed plasmid DNA to shock waves generated with a piezoelectric shock wave source which does not emit ultraviolet or visible radiation, and found that changing the size of the plasmid from approximately 3000 to 23,000 bp significantly increased the shock wave-induced damage.

After the studies published by Gambihler et al. (1992) and other groups, demonstrating that cells exhibit a transient increase in membrane permeability upon exposure to shock waves, Lauer et al. (1997) investigated whether this phenomenon could support the transfer of plasmid DNA into eukaryotic cells in vitro. DNA/cell suspensions were filled into polypropylene vials and exposed to 250 shock waves ($p^+ = 80$ MPa) generated at 25 kV ($C = 80$ nF) at a rate of 100 shock waves per minute with an experimental electrohydraulic *XL1* shock wave source (Dornier MedTech GmbH). The vials were aligned with the beam axis and positioned so that the *F2* focus was 10 mm above their bottom. The water in the tank was degassed and maintained at about 36 °C. In the first part of the experiment, HeLa cell suspensions were

mixed with a reported plasmid called pRSVβ-gal. This plasmid encodes the cytoplasmic enzyme β-galactosidase. A negative control reporter plasmid (psV-MHBs) encoding the middle surface protein of hepatitis B virus was also used. The results revealed that only shock wave-treated HeLa cells in vials containing pRSVβ-gal were transfected. This demonstrated that eukaryotic cells can take up naked plasmid DNA. The authors suggested that the mechanism responsible for this phenomenon is acoustic cavitation, because gene transfer was completely abolished by exposing HeLa cells mixed with a reporter plasmid to shock waves under a 10 MPa hyperbaric pressure. As a further step, HeLa cell suspensions containing reporter plasmids were exposed to 125, 250, and 500 shock waves to determine the efficiency of shock wave transfection. Cell suspensions were also mixed with variable quantities of plasmids and exposed to 250 shock waves. Finally, the influence of the amount of cells on the efficiency of shock wave-mediated transfection was studied. Increased numbers of shock waves resulted in an increase in reporter protein expression and in a decrease of viability rates of 80, 65, and 50 % at 125, 250, and 500 shock waves, respectively. Irrespective of the reporter plasmid used, transfection was reported to be proportional to the concentration of DNA (up to 90 μg/ml). It was observed that variations in cell concentration did not alter the overall efficiency of transfection. In the second part of the study, three different cell types of human origin (liver cells, hepatoma cells, and HeLa cells), as well as mouse fibroblast cells, mouse lymphocytic leukemia cells, and monkey kidney cells, were mixed with reporter plasmid and exposed to 250 shock waves. The efficiency of shock wave-mediated transfection varied significantly from one cell type to another. As a final conclusion, the authors commented that their results indicate a general applicability of shock wave permeabilization for the transfer of plasmid DNA into eukaryotic cells.

Bao et al. (1998) studied shock wave-mediated gene transfection by searching for DNA transfer in growing mouse tumors in vivo. The authors also performed in vitro experiments to study shock wave transfection. Mouse melanoma cells were cultured and implanted subcutaneously in mice 10–14 days before shock wave treatment with an *HM3*-based shock wave source (Dornier MedTech GmbH). A luciferase reporter vector was used as the DNA plasmid for intratumoral injection. In some tumors air was injected after the DNA. This enhanced cavitation and significantly increased shock wave-induced transfection. The achieved luciferase expression (in terms of production per 10^6 cells) was higher in vitro than in vivo. In most shock wave-treated tumors the reporter expression persisted for at least one day. The results confirmed that in vitro and in vivo shock wave-mediated transient transfection of genes into melanoma cells is possible.

The uptake of calcein and fluorescein isothiocyanate-dextran into human leukemia cells after exposure to a single pressure pulse using three different sources: argon fluoride excimer laser, ruby laser, and a shock tube was investigated by Kodama and coworkers (2000). The duration of the pressure pulse emitted by the shock tube was approximately 100 times longer than the duration of the shock waves produced by the lasers. Intracellular fluorescence measurements with a spectrofluorometer and examination by confocal fluorescence microscopy revealed that the shock tube delivered both fluorophores into approximately 50 % of the cells,

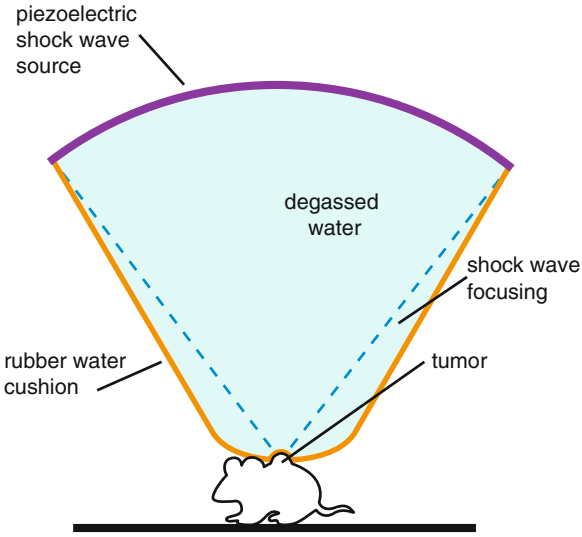


Fig. 7.5 Sketch of a research piezoelectric shock wave source used for in vivo exposure of human tumors implanted on the back of nude mice. Adapted from Kato et al. (2000)

whereas shock waves from the lasers did not. An interesting conclusion of this study was that the impulse of the shock waves, i.e., the pressure integrated over time, and not the p^+ value, is significant for molecular delivery into living cells.

Kato et al. (2000) implanted a human colon cancer cell line onto the back of nude mice. Two thousand shock waves ($p^+ = 40$ MPa), generated with an experimental piezoelectric shock wave source, manufactured by Toshiba Co., Ltd., Tokyo, were administered to each tumor (approximately 10×10 mm in size) immediately following an intravenous injection of bleomycin. The overhead shock wave source was filled with degassed water and sealed with a rubber cushion. Acoustic gel was used to assure good shock wave coupling. Each tumor was placed at the focus of the shock wave source (Fig. 7.5). The tumors were excised at different times after shock therapy, to detect cell proliferation and apoptosis. The maximum apoptotic index was observed 6 h posttreatment. According to the results, shock waves enhanced the antiproliferative and pro-apoptotic effects of bleomycin in solid tumors in vivo.

In another interesting study, Delius and Adams (1999) transferred ribosome inactivating proteins (gelonin and saporin) into the cytoplasm of mouse leukemia cells, mouse fibrosarcoma cells, and human cervical cancer cells by in vitro shock wave exposure, and demonstrated that shock waves enhance the cytotoxicity of gelonin and saporin by four orders of magnitude. Shock wave-mediated transfer of the two ribosome inactivating proteins was also tested in a murine tumor model in vivo. Fibrosarcoma tumors grown in mice were exposed to shock waves after intraperitoneal administration of gelonin or saporin. The treatment reduced tumor growth, and long-term reductions lasting more than six months were achieved in 40 % of the animals. No effect on the growth of tumors was observed in shock wave-treated tumors without toxin and in groups with toxin administered without shock wave treatment. An experimental *XL1* shock wave generator (Dornier MedTech GmbH) was used in both the in vitro and the in vivo studies. In the same year, the

in vitro transfection efficiency of HeLa cells with b-galactosidase and luciferase plasmid DNA reporter using either shock waves or focused sinusoidal ultrasound was compared by Huber et al. (1999b), using the same concentrations of plasmid and cells, and the same surrounding conditions. The electromagnetic shock wave source of a *Lithostar* (Siemens Healthcare GmbH), operated at 13, 16, or 19 kV was used to apply between 60 and 360 shock waves at a rate of 1 Hz to cell suspensions positioned at the focus of the device. According to the pressure measurements done by the authors with a calibrated membrane hydrophone (Granz 1989), the peak-positive and peak-negative pressure amplitudes at the focal spot of the shock wave source were approximately 70 and −13 MPa, respectively. Pulsed ultrasound was generated by a single focus piezo-ceramic air-backed disk transducer with a 100-mm diameter at a frequency of 1.18 MHz. The pressure amplitude in the focus varied from 0.1 to 5 MPa. Total sonication times between 10 s and 10 m were used and the pulse repetition frequency was varied from 1 to 500 Hz. The intensity at the focus was approximately 33 W/cm^2 at 1 MPa peak pressure. Compared to control cell suspensions mixed with DNA only, shock wave-exposed suspensions mixed with DNA produced about eight fold more transfected cells at a cell viability of 5 %, whereas ultrasound induced up to 80-fold more transfected cells at a cell viability of 45 %. This data should not be directly transferred to in vivo conditions. The authors concluded that it would be interesting to study, whether shock wave-mediated transfection efficiency changes by reducing or increasing acoustic cavitation. Cavitation could be enhanced by changing the shock wave rate. Another possibility to enhance the transfection efficiency could be the use of tandem shock waves (Lukes et al. 2016). This has been demonstrated for bacteria (Sect. 7.5) (Loske et al. 2011) and filamentous fungi (Sect. 7.6) (Loske et al. 2014). As will be discussed later in this section, Michel and colleagues (2004) also compared shock waves and ultrasound as possible transfection methods.

Zhong and colleagues (1999a) studied cell membrane permeabilization and injury to mouse lymphoid cells by exposing polyethylene vials containing suspensions of cells and fluorescein isothiocyanate (FITC)-labeled dextran to shock waves generated with an *XL1* experimental electrohydraulic shock wave source (Dornier MedTech GmbH), equipped either with the standard reflector or a modified (composite) reflector. The modified reflector consisted of a 28-mm thick annular brass ellipsoidal ring reflector mounted on the aperture of a standard *XL1* reflector (Fig. 7.6). The ring reflector had six segments, which could be mounted independently on the *XL1* reflector. The *F1* and *F2* foci of both the *XL1* and the ring reflector coincided; however, the ring reflector had a 15 mm shorter major axis. As a consequence, a small part of the shock wave generated at *F1* was reflected off the annular ring, generating tandem shock waves (Sect. 4.7), i.e., a weak leading pressure pulse that reached *F2* approximately 8.5 μs before the main shock wave ($p^+ = 62$ MPa, $p^- = -15$ MPa). The pressure of the preceding pressure pulse could be varied depending on the number of segments mounted on the rim of the *XL1* reflector. Pressure records revealed that the peak-negative pressure of the first shock wave could be varied between about −1 and −2 MPa (discharge voltage 20 kV). This leading shock wave induced the expansion of microbubbles in the vicinity of *F2*.

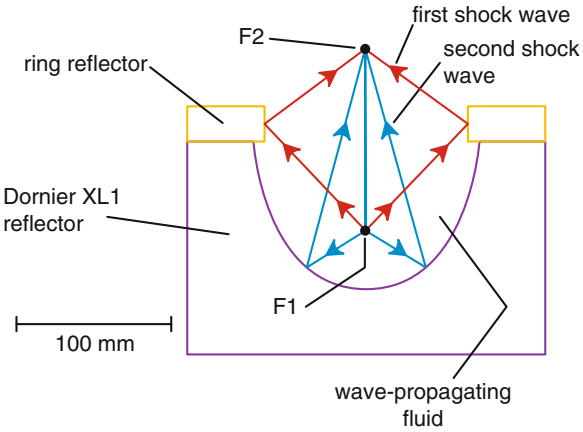


Fig. 7.6 Schematic of a composite reflector consisting of an annular ring reflector mounted on the rim of an *XL1* experimental shock wave source (Dornier MedTech GmbH, Wessling, Germany). Adapted from Zhong et al. (1999a)

Enhanced bubble collapse with intense secondary shock wave and microjet emission was detected using membrane hydrophones, shadowgraph imaging, and passive cavitation detection. Under normal conditions, the cultured cells did not take up the FITC-labeled dextran; however, after shock wave exposure, dose-dependent cell membrane permeabilization and cell mortality was observed. Interestingly, there was an optimal combination of the leading and the main shock wave that produced the most efficient cell permeabilization. Applying 50 shock waves (generated at 25 kV), the maximum permeabilization efficiency (15 %) was achieved using only three sections of the annular reflector. At the same shock wave dose, the efficiency produced using the standard *XL1* reflector alone, and the *XL1* reflector with the complete annular ring mounted on top of it, were 7.8 % and 7.4 %, respectively. The results revealed that using tandem shock waves, a significantly enhanced cell injury can be achieved at high exposure (more than 100 shock waves), and an increased membrane permeabilization efficiency can be obtained at low exposure (50–100 shock waves) by selecting an optimal pulse combination. According to these findings, shock wave microbubble interaction may be used either to enhance macromolecular delivery or tissue destruction. By optimizing the design of the annular ring segments, the strength of the first shock wave could be adjusted so that the microbubbles are collapsed near their maximum size. Cell membrane permeabilization may be improved even more by adjusting the delay between the first and the second shock wave; however, a different annular ring would be needed for each delay. Composite reflectors as described in Sect. 5.2.1 (Loske and Prieto 2001) could also be used for tumor therapy because very short delays can easily be generated by an appropriate reflector design. Other authors also reported that, compared to standard lithotripter shock waves, tandem shock waves may cause enhanced cytotoxic effects in tumor cells both in vitro and in vivo (Sokolov et al. 2003).

Huber and Debus (2001) modified an electromagnetic lithotripter to study the interaction of 500 tandem shock waves on Dunning prostate tumors transplanted into the thighs of Copenhagen rats. Shock waves with a peak-positive and peak-negative pressure of approximately 40 and −12 MPa, respectively, were emitted at

delays of 20, 400, and 1500 ms. Pyknotic nuclei, severe intracellular and pericellular vacuoles, and irregular necrosis were observed in the treated tumors. At delays of 20 ms tumor growth was almost two times slower compared to the control group. It was also significantly lower compared to tumors exposed to single-pulse shock waves. Enhanced acoustic cavitation was considered responsible for the increased histopathological changes observed in tumors treated with tandem shock waves. Even if a delay of 20 ms is too long to enhance bubble collapse (Sect. 4.7), it is possible that bubble fragments remaining from the first shock wave were still present as the second shock wave arrived, serving as cavitation nuclei.

The effects of 500 shock waves ($p+\approx 43$ MPa; $p^-\approx -7$ MPa), recombinant interleukin-12 (rIL-12) protein, and DNA plasmid coding for interleukin-12 (pIL-12) were investigated on the progression of mouse melanoma and renal carcinoma tumors implanted and grown on the hind legs of syngeneic (genetically identical) mice by Song et al. (2002). Air bubbles and PBS, either with rIL-12 or pIL-12, were injected into the tumors. The study demonstrated that shock waves followed after air injection delayed the tumor growth for a few days, indicating that cavitation is responsible for the desired effect. pIL-12 injection alone did not reduce tumor growth; however, the combination of shock wave therapy and pIL-12 injection provided a statistically significant reduction in tumor growth relative to shock wave therapy alone. IL-12 expression due to shock wave-mediated gene transfection was confirmed in an enzyme-linked immunosorbent assay (ELISA). Shock waves were generated at a 2-Hz rate with an experimental *HM3*-based lithotripter (Dornier MedTech GmbH).

Miller and Song (2002) evaluated the efficacy of four cavitation nucleation agents (saline, ultrasound contrast agent, a vaporizing perfluoropentane droplet suspension, and air) to improve strategies for simultaneous shock wave-mediated tumor ablation and cancer gene therapy. Renal carcinoma tumor cells were implanted on the hind legs of syngeneic mice. Before shock wave treatment, a DNA plasmid coding for marker proteins was injected into the tumor. The first part of the experiment involved measurement of tumor growth and the use of a beta-galactosidase marker plasmid for localization of transfection. In the second part of the test, a luciferase marker plasmid for assessing overall protein expression was used. Shock waves ($p^+\approx 43$ MPa; $p^-\approx -7$ MPa) were generated with an electrohydraulic lithotripter. Four days after treatment with 500 shock waves, all the nucleation agents reduced the tumor growth about the same amount. Two days after treatment, all nucleation agents, except saline, produced significant increases in luciferase expression, relative to sham exposure. Intravenous injection of Optison or droplet nucleation agents before shock wave therapy reduced the tumor growth; however, it did not increase transfection efficiency.

A year later, Frairia et al. (2003) published the response of a human breast cancer cell line to the combined effect of shock waves and paclitaxel, an antimicrotubular agent which is effective against several types of tumors. Cells were exposed to between 100 and 2000 shock waves (EFD = 0.25 mJ/mm^2; $p^+ = 31$ MPa; $p^- = -4.3$ MPa) at a rate of 4 Hz using a *Piezoson 100* shock wave source (Richard Wolf GmbH, Knittlingen, Germany). The cell viability was determined with trypan

blue dye exclusion. A few days after shock wave treatment, the number of viable cells returned to control levels even when up to 90 % of them had been destroyed. Enough viable cells (more than 70 %) for drug treatment were left after exposure of up to 1000 shock waves. The treatment of cells with both paclitaxel and shock waves resulted in a significant reduction in cell proliferation.

A prototype based on the *Modulith SLK* lithotripter (Storz Medical AG) was used by Schaaf et al. (2003) to study the in vitro transfection of three human bladder cancer cell lines. The goal of this research group was to develop a gene therapy for the treatment of bladder cancer. Suspensions containing 5×10^6 cells per milliliter and green fluorescent protein (GFP) plasmid were placed inside polypropylene vials centered at the focus of the shock wave source and exposed to 500, 1000, and 1500 impulses at energy levels ranging from 0.07 to 0.5 mJ/mm^2. The results showed that higher energies and a larger number of shock waves increased the transfection rate. An increase in the shock wave delivery rate from 2 to 4 Hz also resulted in a transfection efficiency increase. Furthermore, the presence of a liquid–air interface inside the test tube enhanced transformation efficiency, probably because of reflection of the shock waves at the liquid–air interface, which results in additional cavitation.

Michel et al. (2003) assessed in vivo gene transfection by protein expression in a Copenhagen rat prostate cancer model using pEGFP-N1 as a reporter gene and a *Modulith SLK* electromagnetic shock wave generator (Storz Medical AG). Subcutaneously growing tumors were injected with a DNA plasmid solution before shock wave treatment. To enhance acoustic cavitation, air was also injected into the center of each tumor. One group of rats ($n = 8$) received 1000 and a second group ($n = 8$) received 2000 shock waves focused on the center of the tumors (EFD = 0.5 mJ/mm^2) at a rate of 2 Hz. Explanted tumors were recultivated. The survival rate was obtained by cell counting after staining with trypan blue. The transfection rate was assessed by fluorescence-activated cell sorting (FACS), i.e., by an automated flow cytometer that analyzes cells as they pass through a focused laser beam one at a time. The survival rate of shock wave-treated cells ranged between 40 and 60 %. Transfection rates in the sham group were below 0.5 %; however, in the first and second experimental group, the mean transfection rate was 2.6 and 4.6 %, respectively.

Different acoustic waveforms as possible transfection methods for cancer of the prostate, cancer of the bladder, and benign kidney cells were studied by Michel et al. (2004). An electromagnetic source operated at various delivery rates and EFD values was compared with focused ultrasound. The transfection efficiency was evaluated through reporter genes by FACS. Electroporation and transfection by lipofectamine served as controls. The highest transfection rate was obtained with focused ultrasound (200 W, 500 ms), followed by 1500 shock waves emitted at a rate of 2 Hz (EFD = 0.5 mJ/mm^2).

As mentioned before, shock wave-induced microbubble growth and collapse in the vicinity of living cells can affect their membrane permeability. Asymmetric bubble collapse may form high-speed liquid microjets that can cause localized membrane poration. The collision between the inward-moving wall of the bubble

and the microjet generates a secondary shock wave (Sect. 4.7), which contributes to membrane permeabilization. These secondary shock waves interact with other cavitation bubbles or boundaries. They can occur as a consequence of single bubble collapse or due to the interaction between the cloud collapse-induced shock wave and microbubbles situated close to the collapse site of the cloud. Ohl and Ikink (2003) estimated that a microjet is capable of injecting a volume of approximately one tenth of R_0^3, where R_0 is the initial bubble radius before the arrival of the shock wave. Even if the peak pressures of secondary shock waves can be very high, most of the energy is dissipated within short distances (about 100 μm) from the bubble (Brujan et al. 2008). Bekeredjian et al. (2007) studied the impact of microbubbles on shock wave-mediated DNA uptake in cells in vitro. Ohl et al. (2006) focused shock waves on a Petri dish with layers of adherent cells attached to the surface and were able to demonstrate that cavitation bubbles and not the shock waves directly are responsible for drug delivery. Shock wave-induced cavitation has also been useful for in vitro cell detachment. Interesting results revealing that the standard techniques of cell detachment by mechanical or chemical methods could be substituted by shock wave exposure were reported in 2003. Using a *Piezolith 3000* shock wave source (Richard Wolf GmbH), the research team was able to detach cells from a substrate after application of a single shock wave and showed that fluid microjets produced during bubble collapse directed at the rigid boundary of the culture flask were responsible for the detachment (Junge et al. 2003).

In vitro membrane poration has been achieved not only by multiple bubble collapse in cell suspensions but also by single bubble collapse on single cells. These experiments are crucial to better understand the phenomena involved in shock wave transfection. Le Gac et al. (2007) combined sonoporation based on a single laser-induced bubble and microfluidic confinement to porate cells. The cells were introduced in a microchamber and submitted to the growth and collapse of a single bubble. Loss of cell membrane integrity was evaluated by measuring either the release of previously loaded calcein or by the uptake of trypan blue. A hypothesis is that bubble-induced flow exerts shear stress on the cells, leading to the rupture of their membrane.

Sankin et al. (2010) developed an interesting method to produce pores on single cells by generating tandem microbubbles. To generate two bubbles via optical breakdown in the vicinity of a single cell, two 5 ns Q-switched neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers were focused through a 63× microscope objective into a 25 μm fluid gap containing 0.4 % trypan blue. The microfluidic channel was obtained with two 25-μm platinum wires placed in parallel in a Petri dish to form a channel of approximately 10 by 25 mm. A glass plate was placed on top of the platinum wires to close the chamber. Trypan blue was used not only because it provides a marker to assess membrane poration, but also because it enhances laser absorption, facilitating optical breakdown. Rat mammary carcinoma cells were trypsinized and reseeded one day before the experiment. When cell growth reached about 10 % confluence, the culture medium was replaced by saline solution containing 0.4 % trypan blue. The laser pulses were released with a 4 μs delay. The first bubble expanded to a maximum size (~50 μm) before the second

bubble was produced, that is, the collapse of the first bubble was coupled with the expansion of the second bubble, leading to the formation of alternating, directional microjets in opposite directions. The authors observed entrance of trypan blue from the cell surface proximal to the jet impact in 6 s. The dye diffused in the cytosol in about 24 s. Staining of the cell nucleus occurred after 42 s. The size of the pores could be varied from nanometer to micrometer range; however, no pores were formed when the cell was placed more than 10 µm off a line joining both microbubbles, or when the cell was on the tandem bubble axis with a stand-off-distance greater than 40 µm. Hsiao et al. (2013) developed numerical models to study the features of the above mentioned bubble oscillations in a narrow fluid gap confined by two parallel solid boundaries.

Canaparo et al. (2006) studied the in vitro effects of shock waves on human colon cancer cells exposed to 5-aminolevulinic acid (ALA). Aliquots of 1 ml (1×10^6 cells/ml) were placed into 2-ml polypropylene tubes, completely filled with culture medium and pelleted by centrifugation before shock wave treatment. A water-filled cushion and ultrasound gel were used to couple the shock waves generated with a *Piezoson 100* (Richard Wolf GmbH) into the test tubes (Sect. 6.2). Two intensity settings (EFD = 0.22 mJ/mm^2; $p^+ = 31$ MPa and EFD = 0.88 mJ/mm^2; $p^+ = 90$ MPa) and two numbers of shock waves (500 and 1000) were tested at a fixed rate of 4 Hz. Cell viability was analyzed with trypan blue dye exclusion. After exposure to 1000 shock waves at an EFD of 0.88 mJ/mm^2, the cell viability decreased to 30 % with respect to cells in the untreated control group; however, the number of viable cells returned to control levels after a few days. A significant reduction of cell growth after ALA and shock wave treatment was observed only after 500 shock waves at an EFD of 0.88 mJ/mm^2. The results revealed that after ALA treatment only 1000 shock waves at an EFD of 0.22 mJ/mm^2 produced intracellular sensitizer radicals, whereas extracellular production of free radicals by pyrolysis of the water vapor inside the bubble was observed after 500 shock waves at an EFD of 0.88 mJ/mm^2. The authors concluded that shock waves may be proposed for cancer treatment, as they are able to overcome some drawbacks encountered during conventional ultrasonic and/or photodynamic treatment.

The search of new treatments for patients suffering from osteosarcoma (bone tumor) led Palmero et al. (2006) to study new ways to increase the chemo-sensitivity of osteosarcoma cells. Cell suspensions were placed into polypropylene tubes and exposed to shock waves generated with a *Piezoson 100* (Richard Wolf GmbH). Proper shock wave coupling was assured by means of a water-filled cushion and ultrasound gel. Cells were exposed to 1000 shock waves at a rate of 4 Hz (EFD = 0.22 mJ/mm^2, $p^+ = 31$ MPa; $p^- = -4.3$ MPa). According to their results, shock waves may enhance the cytotoxic effect of doxorubicin and methotrexate to human osteosarcoma cell lines and modify the cell growth of tumors; however, a main concern about the treatment of malignant tumors with shock waves is the potential development of metastases.

The hypothesis that addition of DNA-loaded microbubbles increases transgene expression in shock wave-exposed tissue culture cells, compared with cells that were exposed to DNA and shock waves without microbubbles was studied by

Bekeredjian et al. (2007). Cell suspensions with or without lipid-stabilized microbubbles, produced as described in an earlier publication by the same research group (Bekeredjian et al. 2003), were treated with 60–120 shock waves generated at different energies (p^+ between 7 and 48 MPa; p^- between −5 and −10 MPa) with an *Epos* ESWT system (Dornier MedTech GmbH). After 80 shock waves at the highest energy level all microbubbles were destroyed; however, a significant percentage of microbubbles were still present after 120 shock waves at lower energy settings. The results revealed that the presence of microbubbles increased transgene expression in tissue culture cells exposed to both plasmid DNA and shock waves; however, higher cell death rates were found when using microbubbles. It seems reasonable to believe that the presence of microbubbles increases the number of cavitation nuclei and cavitation events in the sample. Increased transgene expression was obtained at low shock wave energies compared with high energies. Even if these results were encouraging, the authors concluded that the destructive effect of shock waves combined with microbubbles does not warrant gene delivery in tissues. According to their findings, the technique should rather be considered for treatment of tumors where cell death is the final goal.

Mastikhin et al. (2010) reported interesting results on the combined action of shock waves and chemotherapy to inhibit tumor growth both in vitro and in vivo. The reaction of mice Krebs-2 tumor cells to a drug used in chemotherapy (cyclophosphan) was analyzed after exposure to shock waves or sham treatment (no shock waves). Shock waves were generated with a portable desktop electromagnetic source with acoustic lens developed at the Lavrentiev Institute of Hydrodynamics (Novosibirsk, Russia). In the first part of their study, cells in suspension were exposed to between 5 and 70 shock waves ($p^+ = 45$ MPa) at a rate of 0.2 Hz, and injected into the feet pads of mice. Thirty minutes after inoculation the animals received an intraperitoneal injection of cyclophosphan. Mice were sacrificed 12 days later to analyze the tumors and determine their mass. After the tumors reached about 5 mm in diameter, mice were divided into a control (sham) group, a shock wave group, and several combined-treatment groups. Tumors were analyzed seven days after treatment. The results of the first part of the experiment showed that the combination of cyclophosphan and shock waves significantly inhibited tumor growth, compared with single cyclophosphan therapy or shock wave treatment only. It is noteworthy that the inhibition with respect to the number of shock waves was nonlinear, having a maximum between 10 and 20 shock waves. Because the in vitro shock wave treatment excludes phenomena associated with circulation and tissue damage, the nonlinearity suggests that shock waves modify the structure and function of the cells. In vivo, the combination of cyclophosphan and shock waves was also significantly more efficient in reducing tumor growth. Remarkably, shock wave-treated tumors weighted more as compared with sham treated tumors. Furthermore, the smaller number of applied shock waves (10 pulses) was more effective in tumor growth inhibition than a higher dose. The authors concluded that the combination of chemotherapy with shock wave application may enhance the efficiency of chemotherapy and that the effects of shock wave action were significant at cellular and tissue level as well.

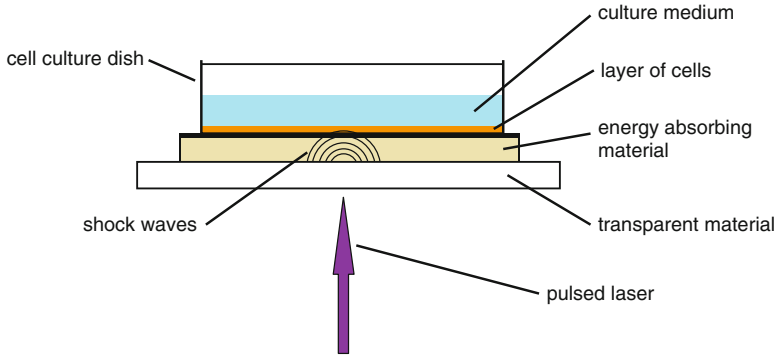


Fig. 7.7 Schematic of an experimental setup as used by Steinhauser and Schmidt (2014), and other research groups to transfect cells. By irradiating the absorbing layer with a laser, the optical energy deposited is transformed into mechanical energy. A shock wave forms and propagates through the absorbing layer into the cell culture dish. Plasmid DNA contained in the culture medium penetrates into the cells through transient holes

Different laser-assisted gene transfection methods, such as optoinjection, photochemical internalization, selective cell targeting with light-absorbing particles, and transfection by laser-induced stress waves (LISW), have been tested in the past (Yao et al. 2008). During LISW a large number of cultured cells are exposed simultaneously to stress waves experiencing transient plasma permeability (Terakawa et al. 2004). By illumination of an absorbing material with a laser, optical energy is transformed into mechanical energy and a shock wave travels into a vessel containing the cells (Fig. 7.7). No precise instrumentation for cell targeting is needed and peak-positive pressure amplitudes up to 100 MPa can be obtained with laser beam diameters of a few millimeters (Steinhauser and Schmidt 2014).

Lasers have also been successfully tested to porate single cells. Myeloma cells suspended in trypan blue saline solution were trapped one by one into a microfluidic chip. A cavitation bubble was created close to a trapped cell with a single Nd:YAG laser pulse. High-speed photography showed that the cell was pushed towards the chip during bubble expansion. A few microseconds later, the bubble contracted, collapsed, and emitted a microjet which porated the cell. The cell membrane recovered its original shape very fast. Trypan blue diffused into the cytosol for approximately half a minute. It was also demonstrated that membrane poration depends on the distance between the cell and the bubble (Li et al. 2012).

A limitation of shock wave-mediated cell transfection with naked DNA that excludes clinical application is the high amount of required nucleic acid (Tschoep et al. 2001). Even if high transfection efficiencies have been reported in human cells using DNA and liposomes (Morille et al. 2008), the protocols are not always amenable to in vivo applications. Millán-Chiu et al. (2014) studied the use of underwater shock waves to transfect human embryonic kidney (HEK) cells with both cationic lipid-assembled and naked DNA. Enhanced GFP was used as a reporter in a plasmid vector. For fluorescent dye internalization, a solution of either calcein or

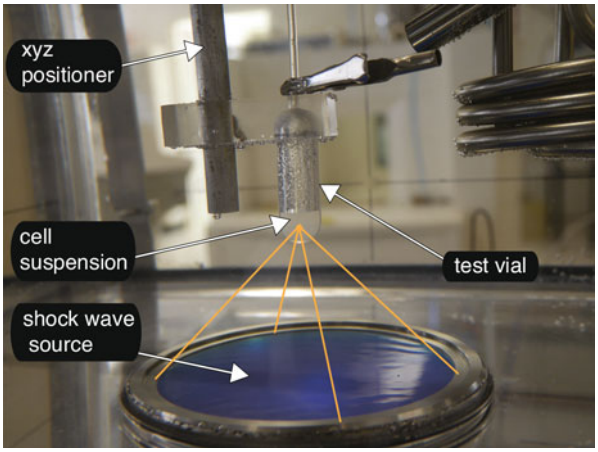


Fig. 7.8 Photograph of a *Piezoson 100*-based research device (Richard Wolf GmbH, Knittlingen, Germany) used to expose cell suspensions to underwater shock waves

neutral FITC-dextran in PBS was mixed with HEK cells. For transfection, a suspension containing 2×10^6 cells was prepared. Naked plasmid was dissolved in purified water and plasmid solution with Dulbecco's Modified Eagle's medium (DMEM), i.e., a medium containing amino acids, vitamins, and glucose was added to the cell suspension before shock wave treatment. Alternatively, self-assembled DNA-cationic lipid complexes were used at an equivalent DNA concentration. Complexes were prepared by incubating the plasmid with a mixture of DMEM and cationic lipids. Cell suspensions were prepared before shock wave exposure and aliquots were placed into polyethylene pipets. A *Piezoson 100 plus*-based experimental device (Fig. 7.8), equipped with a Richard Wolf GmbH *FB10 W3* shock wave source (previous model of the *FB10 G4* shown in the figure), was used to expose the samples to shock waves at a rate of 1 Hz. Three intensity settings (p^+ approximately 8, 12, and 18 MPa) were tested. Increasing both the intensity and the number of shock waves induced cell death in a dose-dependent manner; however, cells exposed to different shock wave energies had identical proliferation profiles after 24 and 48 h. All cell populations produced normal distributions of fluorescence intensities from basal signals to a shift in fluorescence, indicating that the FITC-dextran was incorporated. Control cells only showed a mild fluorescence at their surface when observed with confocal microscopy; however, shock wave-treated cells revealed fluorescence within the cytoplasm, demonstrating that macromolecular internalization was achieved (Fig. 7.9). The main conclusion of this study was that shock waves and lipoplexes acted in a synergistic manner to increase GFP expression levels in HEK cells.

A treatment modality that has been used for some cancer patients is the photodynamic therapy (PDT). A tumor-localizing photosensitizer such as ALA is administered to the patient and activated by light (Peng et al. 1997). Due to the low

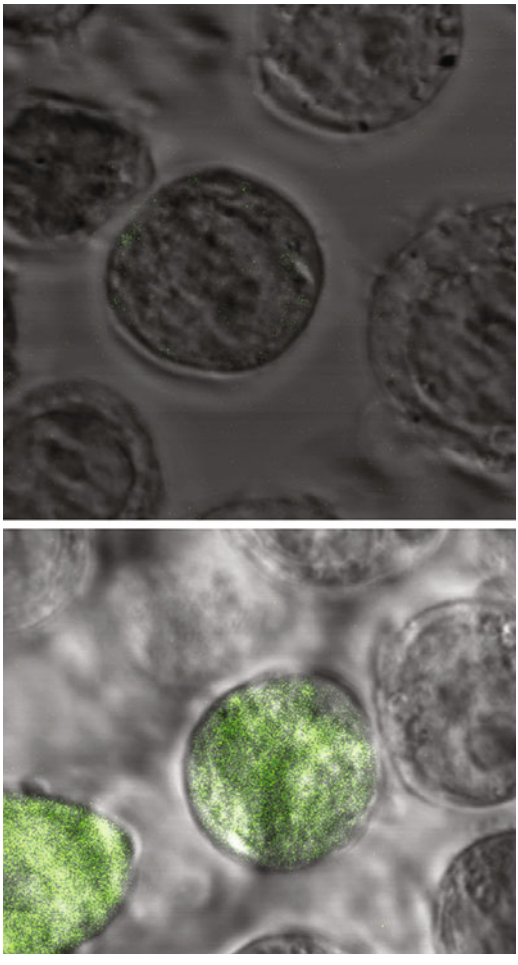


Fig. 7.9 Confocal images of sections taken at the geometrical center of cells incubated with a fluorescent dye showing that the dye (green color in the *eBook*) was internalized in the shock wave-treated samples (*bottom image*) but not in the non-shock wave-treated cells (*top image*)

penetration depth of light through tissues, the technique is limited to the treatment of endoscopically reachable tumors. This drawback does not exist if sonodynamic therapy (SDT), that is, ultrasound is used instead of light. SDT is based on the activation of a sonosensitizer agent by ultrasound-induced cavitation. After being activated, the sonosensitizer, which includes porphyrins and their derivatives, generates reactive oxygen species which may lead to cancer cell death (Umemura et al. 1990; Rosenthal et al. 2004; Kuroki et al. 2007; Tachibana et al. 2008; Song et al. 2014; Costley et al. 2015; Feng et al. 2015). The methodology has also been tested using shock instead of ultrasound waves. Shock wave-induced sonoluminescence is able to produce electronic excitation of porphyrins by energy transfer and initiate a photochemical process leading to the formation of the cytotoxic singlet oxygen. Bubble collapse can result in pyrolysis of the water vapor inside the bubble, generating hydroxyl radicals and hydrogen atoms. The phenomenon is influenced by the

biological model, the sonosensitizer, the EFD, the number of applied shock waves, and the shock wave rate.

The effect of shock waves on the sensitivity to paclitaxel and ALA treatments of two different anaplastic thyroid cancer cell lines was reported by Catalano et al. (2007). Cells treated with ALA and paclitaxel were exposed to 500 shock waves (EFD = 0.88 mJ/mm^2; p^+ = 90 MPa) generated at a rate of 4 Hz with a *Piezoson 100* piezoelectric shock wave source (Richard Wolf GmbH). Aliquots of cell suspension were placed into small polypropylene tubes and filled with culture medium. Cells were pelleted by centrifugation before shock wave treatment. This was done to reduce the motion during shock wave passage through the test vial. Each tube was positioned vertically (aligned with the beam axis of the shock wave source) so that the focal spot of the *Piezolith 100* coincided with the center of the tube bottom. Cell viability and apoptosis were evaluated. The authors reported that the use of ALA, paclitaxel, and shock waves resulted in an enhanced cytotoxicity compared with cells treated only with paclitaxel. An increased induction of apoptosis in thyroid cancer cells with respect to cells treated with paclitaxel alone was also observed.

Serpe et al. (2011) studied the efficacy of ALA and shock wave therapy in vitro on rat colon cancer cells and in vivo on a syngeneic colon cancer model. The in vivo treatment was initiated eight weeks after cancer cell implantation. Rats in the control and in the shock wave-treated groups were sacrificed 24 h after shock wave treatment. Shock waves were applied with a *Piezoson 100* (Richard Wolf GmbH). The in vivo results showed enhanced apoptosis in tumor tissues one day after treatment with ALA (375 mg/kg i.v.) and shock wave therapy (500 shock waves; EFD = 0.88 mJ/mm^2) compared to injection of ALA alone. This confirmed that a combined ALA and shock wave therapy is effective in inducing apoptosis on a colon cancer model.

The potential of poly-methyl methacrylate core-shell nanoparticles loaded with meso-tetrakis (4-sulfonatophenyl) porphyrin as a sonosensitizing system was studied on a human neuroblastoma cell line by Canaparo and coworkers (2013). The cells were exposed to 500 shock waves (EFD = 0.43 mJ/mm^2) at a rate of 4 Hz with a *Piezoson 100* (Richard Wolf GmbH). A significant decrease in cell proliferation was observed after the sonodynamic treatment. The authors also report a 15-fold increase in reactive oxygen species production at 1 h for cells exposed to the sonodynamic treatment compared with untreated cells. The sonosensitizing technique also significantly decreased the neuroblastoma spheroid growth in an in vitro three-dimensional model.

In an in vivo experiment, Foglietta et al. (2015) activated the cytotoxicity of protoporphyrin IX using shock waves to cause death in the rat mammary adenocarcinoma cell line Mat B III. Tumors of approximately 500 mm^3 in volume received 500 shock waves (EFD = 0.88 mJ/mm^2) at a rate of 4 Hz using a *Piezoson 100* (Richard Wolf GmbH). A decrease of about 60 % in tumor size was detected after 72 h in the shock wave-treated group by magnetic resonance imaging (MRI). An increase in diffusion coefficients between pre- and post-therapy and an increase in necrotic and apoptotic histological features 72 h after shock wave SDT were also demonstrated. No blood vessel injury and/or blood cell extravasation was observed in the shock

wave-treated tumors. The authors concluded that the use of shock waves to activate sonosensitizers leading to cancer cell death at different depths in the body is a promising therapy.

As described in Sect. 4.7, when using tandem shock waves with delays between approximately 200 and 800 μs, the bubble collapse induced by the first shock wave is intensified by the second shock wave. This phenomenon may cause enhanced cell membrane permeabilization. For very short tandem shock wave delays (approximately 10–15 μs), the bubbles produced by the first shock wave have insufficient time to grow before arrival of the second pulse. According to Lukes et al. (2014), in this case, the first shock wave can be used to locally change the acoustic properties of a tumor. If a second shock wave arrives at the tumor between 10 and 15 μs after the first shock front, its velocity of propagation is different than in the non-shock wave-treated tissue. Because of this, it propagates with growing strength through the tumor. The effect was studied with the multichannel discharge shock wave source described in Sect. 5.5.4 on different cancer cells and tumors using various animal models (Sunka et al. 2006; Benes et al. 2007, 2011, 2012; Lukes et al. 2012b, 2014). The peak-positive and peak-negative pressure of the first and second shock wave was approximately 35 and −25 MPa, and 80 and −75 MPa, respectively. The delay between first and second shock wave was fixed at 10 μs and the repetition rate used was 0.7 Hz. Tandem shock waves were focused on the liver and tight muscles of rabbits in vivo. Shock wave-treated regions were examined by MRI. Tissue damage was approximately two times the −6 dB focal size of the shock wave source. A histological analysis showed a sharp boundary between the necrotic and the healthy tissue. Tandem shock wave-induced in vivo tumor growth delay was studied with B16 melanoma, T-lymphoma, and R5-28 sarcoma cells. Mice and rats were used as animal models. Tumors were transplanted into the flanks or thighs of the animals. Results revealed that tandem shock waves significantly delayed tumor growth, compared to the control groups. Increasing the number of tandem shock waves above 400 resulted in tissue damage of tumors. Combining the shock wave treatment with cisplatin treatment reduced the tumor growth by three times that of the controls. This effect is supposed to be due to increased permeability of the cancer cell membranes. Further studies showed that tandem shock waves in combination with Photosan reduced tumor growth significantly. Photosan is a sonosensitive porphyrin-based photosensitizer used in photodynamic cancer therapy. The drug preferentially accumulates in malignant tissue and is nontoxic in the absence of light or ultrasound; however, it leads to the formation of cytotoxic singlet oxygen when it is excited sonochemically. The observed effect has been associated with enhanced acoustic cavitation, which induces sonochemical excitation in the tumor. To elucidate the potential of short-delay tandem shock waves to treat cancer, more research is needed to find the optimal shock wave profile and the time delay between the first and second shock wave.

The results of most in vitro experiments, exposing cancer cells to underwater shock waves at energies used in clinical applications, are promising. Shock wave-induced sonochemical effects, cavitation-enhanced cytotoxicity, and cell transfection using several shock wave sources, cell types, and protocols have been reported

for many years. Unfortunately the transfection efficiency in vivo generally is lower than in cell suspensions, because as mentioned before, fewer cavitation nuclei exist in blood or tissue.

Methods for simulating biological systems have proven to be helpful to understand the interaction of shock waves with cells. Koshiyama et al. (2006) performed molecular dynamics (MD) simulations of lipid bilayers of cell membranes subjected to the action of shock waves, concluding that shock wave-induced damage to cell membranes produces structural changes in the phospholipid layer, allowing the permeation of water molecules. Numerical simulations using MD have also been helpful to reveal the mechanism of transient poration in lipid bilayers by shock-induced collapse of nanobubbles. Steinhauser and Schmidt (2014) studied laser-induced shock wave effects on cells, and applications of multiscale modeling to explore the interaction of shock waves with soft biological matter. A useful approach to analyze shock wave-induced damage to cancer cells and reduce the complexity of the calculations was to concentrate on the plasma membrane and the cytoskeleton, a network of macromolecules, which provides structural integrity and protects the cell from external forces.

As mentioned before, cavitation-mediated cell transfection depends on several factors. One of them is the size of the bubble before shock wave exposure. To better understand the effects involved in membrane poration by shock wave-induced nanobubble collapse, Adhikari et al. (2015) performed MD simulations. Their results showed that the shock wave hits the membrane and is followed by a nanojet emitted by the collapse of a nanobubble. Interestingly, in the absence of a bubble, the shock pressure is evenly distributed along the lateral area of the cell membrane and the shock wave is not capable of producing damage to it. Furthermore, they found that the size of the pores depend on the velocity and on the duration of the shock wave. According to these numerical simulations, pores of various sizes could be produced by adjusting these two parameters.

Lukes and colleagues investigated shock wave-induced effects in tumor tissue in vivo. Lewis rats with syngeneic sarcoma were exposed to shock waves ($p^+ \approx 370$ MPa, $p^- \approx -17$ MPa) generated with a multichannel discharge shock wave source (Sect. 5.5.4). Tumor tissue samples were analyzed using several techniques. The authors found extensive damage on cryosections from shock wave-treated tumor tissue and concluded that the damage observed was caused mainly by mechanical stress and shear forces (Lukes et al. 2014, 2015).

Menezes and coworkers (2012) developed a device that emits a plasma jet to deliver microparticles into soft living targets for transferring biological agents. Gold particles of 1 μm size were coated with the desired plasmid DNA and deposited on one surface of an aluminum foil. The laser ablation of the foil generated a shock wave, followed by a plasma jet that carried the particles into the living cells at an average velocity of 1100 m/s. An advantage of the device is that it can be miniaturized into a hand-held drug/DNA delivery device for biological applications. Biocompatible gold, silver, or titanium foils could be used instead of aluminum during delivery of drug into soft, internal targets in the human body.

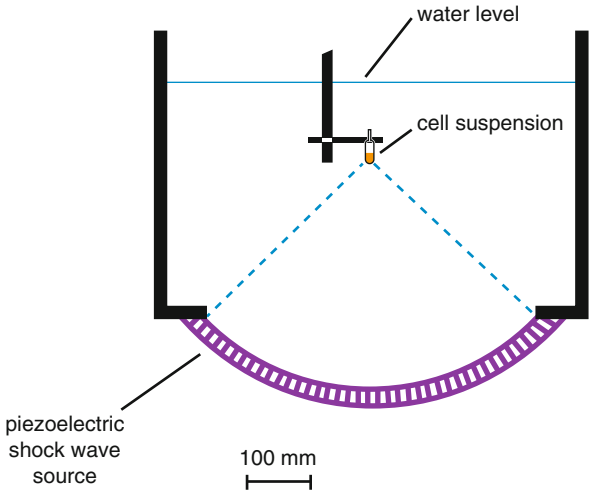


Fig. 7.10 Schematic of a setup to transfect human cells in vitro. Test vials containing cell suspensions are positioned at the focal spot of a piezoelectric shock wave source

Another interesting approach involves small shock wave sources designed to be inserted into the patient through a trocar or a natural orifice. They may be used in the future to directly access target tissues. Nakagawa et al. (2012) developed a small electrohydraulic shock wave source for gene transfection. Their device uses a half ellipsoidal reflector (outer diameter 11 mm) to focus shock waves generated by an underwater high-voltage electric discharge (between 1 and 5 kV) at the inner focus (*F1*). The distance from the edge of the reflector to the outer focus (*F2*) is 10 mm. The system was used by the authors to transfect mouse embryonic fibroblast cells with 10 shock waves ($p^+ = 2.1$ MPa) generated at 4 kV.

As a contribution to the understanding of shock wave-induced effects on human cells, HEK and human breast adenocarcinoma cells have been exposed to underwater shock waves in vitro. Cell suspensions were placed inside polyethylene pipettes at the focus of a *Piezolith 2501*-based (Richard Wolf GmbH) research shock wave generator (Fig. 7.10). Scanning electron microscopy (SEM) revealed the loss of microvilli, the presence of hole-like structures, and a decrease in cell size after exposure to shock waves ($p^+ \approx 18$ MPa; $p^- \approx -3$ MPa) generated at a 0.5 HZ rate. HEK cells received 60, 120, and 180 shock waves and vials containing breast adenocarcinoma cell suspensions were exposed to 125, 250, 500, and 1000 shock waves. A fluorescent dye was used to qualitatively assess cell membrane permeabilization. Trypan blue exclusion assays showed that membrane poration occurred, but was resealed after a few seconds. Deformations produced to the cell membranes lasted more than 5 min and could be observed in fixed cells. Interestingly, the number of shock waves required to obtain membrane poration and gene transfection was different for each cell line. The outcome of this study reveals that shock waves produce transient nano- and micro-sized membrane deformations, allowing cell transfection. Furthermore, it reveals that shock wave parameters should be matched to each cell type in order to optimize the results, because it seems that acoustic cavitation and shear stress act at different extents depending on the properties of the cell membrane (López-Marín et al. 2016).

In spite of all the evidence that acoustic cavitation is responsible for cell transfection, there are also experimental results revealing that other mechanisms seem to be involved. siRNA is known as a therapeutic agent for various diseases because it can inhibit target gene expression in mammalian cells. Ha et al. (2015) reported results of shock wave-induced gene transfection, both in vitro and in vivo. In their study, human umbilical vein endothelial cells (HUVECs) incubated for up to 5 min after exposure to shock waves were not transfected with siRNAs, whereas the same cells incubated for 24 h showed high transfection efficiency. Considering that pores induced by sonoporation have been reported to be resealed in less than 3 min (Zhou et al. 2008), the authors conclude that if the mechanism of gene transfection was sonoporation, transfection would have occurred immediately after shock wave treatment. Their results indicate that shock waves induce the secretion of microparticles of various sizes, which acted as siRNA carriers. Based on their findings gene transfection occurred via the secreted microparticles. Additionally, they observed that particles larger than 200 nm were capable of taking up a greater quantity of siRNAs than smaller particles. Confluent cells were cultured and exposed to 1000 shock waves (EFD = 0.04 mJ/mm^2) using an *AR2* ESWT device (Dornier MedTech GmbH) by perpendicularly immersing the shock wave source into the well plate such that it contacted the surface of the medium. Cells were harvested after shock wave exposure and were subjected to Western blot analysis, a technique to detect proteins by gel electrophoresis. Transfection of siRNAs was observed by fluorescence microscopy. In the in vivo experiment, the authors studied whether shock wave-delivered siRNA into tumors has an inhibitory effect. Mouse carcinoma cells in PBS were inoculated subcutaneously into the lower flanks of nude mice. When the tumors had reached a volume of about 1 cm^3, they were injected with a vascular endothelial growth factor (VEGF) siRNA solution and treated with 1000 shock waves at an EFD of 0.02 mJ/mm^2, using the above mentioned shock wave source. This shock wave dose was optimal for successful transfection of siRNAs into the tumors. The shock wave-treated group showed very low expression of VEGF compared with the control tumor group that did not receive shock wave therapy. Tumors exposed to shock waves exhibited decreased microvasculature, whereas non-treated tumors showed high microvascular density.

7.5 Bacterial Transformation

For prokaryotic cells, the uptake of naked DNA from the environment is called genetic transformation. The DNA can be incorporated into the genome or it can survive as a plasmid. Internalization of exogenous DNA allows a bacterium to adapt to a variety of changing environments. A well-known example is antibiotic resistance. Today, about 80 species are known to be naturally transformable (Johnston et al. 2014).

The growing interest in biotechnology requires new methodologies to genetically transform microorganisms. Bacterial transformation is important in molecular biology and a fundamental tool in environmental microbiology, agriculture, the

enzyme industry, and the pharmaceutical industry; nevertheless, there is still a lack of efficient and easy-to-use DNA transfer methods for gene delivery (Boucher et al. 2001; Demain and Vaishnav 2009; Aune and Aachmann 2010).

Bacteria can be genetically modified by conjugation, transduction, or transformation. Conjugation is the natural process by which DNA is transferred from one bacterium to another, either by direct contact or by a bridge connection between the two cells. Interestingly, the genetic information transferred is commonly beneficial to the bacterium that receives it. An example is the resistance to certain antibiotics, transferred from a donor bacterium to a recipient bacterium. Transduction is the transfer of genetic material by a virus. As mentioned above, the third process, i.e., genetic transformation, is defined as the direct uptake of exogenous DNA. In some species it can happen naturally; however, the bacterium must be *competent*. Bacterial competence occurs among Gram-positive and Gram-negative bacteria and allows uptake of macromolecular DNA (Dubnau 1999). It can be a response to various environmental conditions; but only a low percentage of bacterial species can be naturally transformed under laboratory conditions. Transformation is limited by the fact that bacteria have membranes that are impermeable to DNA.

Plasmids play a crucial role in bacterial transformation. A common practice in molecular biology is to use a plasmid that contains resistance to an antibiotic as a vector. A specific gene is inserted into the vector plasmid. As a next step, the plasmid is transferred into bacteria that are sensitive to an antibiotic, for instance, ampicillin. Only bacteria that acquired the plasmid are resistant to the antibiotic and grow on culture dishes containing ampicillin. Since the bacteria need the plasmid to survive they start replicating it, along with the inserted gene.

A bacterium that is known to be naturally capable of transformation is *Bacillus subtilis*. Other important bacteria such as *Escherichia coli* (*E. coli*) do not have this capability and artificial methods are needed to genetically transform them. This is specially important in the case of *E. coli*, because it is one of the most widely used bacteria for the industrial production of many proteins. Its rapid growth rate, fast expression, and ease of culture are advantages over other species.

Another interesting and useful microorganism is *Agrobacterium tumefaciens*, a Gram-negative bacterium capable of transferring a segment from its tumor-inducing plasmid to the host cell genome of a plant, causing a tumor. This natural process involves the transfer of DNA containing a set of oncogenes, which lead to neoplastic growth of the transformed tissue and to the production of substances used by the bacteria as a nitrogen source. If the transferred deoxyribonucleic acid (T-DNA) of *Agrobacterium* is replaced with other genes it is possible to take advantage of the natural transformation mechanism and introduce these foreign genes into plants for the production of transgenic plant species. This process, called *Agrobacterium* mediated transformation (AMT), is the most popular biological transformation method.

Usual physical methods of genetic transformation are electroporation, heat shock, and sonoporation (Boucher et al. 2001; Chen et al. 2005). Commonly, the first step for transformation is to make the bacteria competent by weakening their membranes to make them more permeable. After this, bacteria are exposed to a high-voltage pulse, a heat shock, or ultrasound waves to open the membrane, allowing

DNA to penetrate. As a final step, the cells are incubated under special conditions to enhance their proliferation. Unfortunately, these methods can only be used for a limited number of applications. Conventional methodologies are expensive and inefficient and there are several types of bacteria that cannot be transformed, including important pathogenic species.

Another alternative to achieve a transient increase of the cell membrane permeability, allowing large molecules to enter the cell, has been the use of underwater shock waves (Jagadeesh et al. 2004; Divya Prakash et al. 2011; Loske et al. 2011). As described in the previous section, shock waves have been used to transfect different types of cells, such as melanoma cells, mouse leukemia cells, kidney cells, and bladder cancer cells by increasing the permeability of the cell membrane. Analogously to human cell transfection, the main phenomenon responsible for shock wave-induced bacterial transformation is supposed to be acoustic cavitation. Microbubble collapses inside bacterial suspensions exposed to shock waves, weaken the membranes of the microorganisms allowing the entrance of macromolecules. Shock wave-mediated bacterial transformation has similarities with sonoporation by ultrasound. It has been observed that ultrasound forms cavitation in aqueous solutions, which is supposed to be responsible for the appearance of transient pores of approximately 30–100 nm in bacterial membranes, enabling DNA transfer. The recovery time of the membrane is between a few seconds and a minute (Liu et al. 2006; Newman and Bettinger 2007; Hayer 2010). Future research will help to further elucidate the phenomena involved in shock wave-mediated DNA uptake.

Jagadeesh et al. (2004) transformed competent *E. coli* cells with spherical shock waves, generated by underwater high-voltage electric discharges between two electrodes separated 1 mm (Fig. 7.11). Best results were obtained by adjusting the voltage to obtain a peak-positive pressure inside the test vial of approximately 13 MPa. The transformation efficiency obtained in the shock wave-exposed vials was significantly higher compared to the standard chemocompetent bacterial transformation method. The vials containing the bacterial suspension were placed at 3 mm from the spark-plug, that is, no reflector was used to concentrate the shock waves. The test vials were also exposed to the strong visible and ultraviolet radiation emitted by the high voltage underwater discharge.

A device to generate unfocussed shock waves using a 300-mm-long explosive-coated polymer tube has also been used to transform *E. coli* (Fig. 7.12). The transformation efficiency was about 10 times higher than using ultrasound. *Pseudomonas*

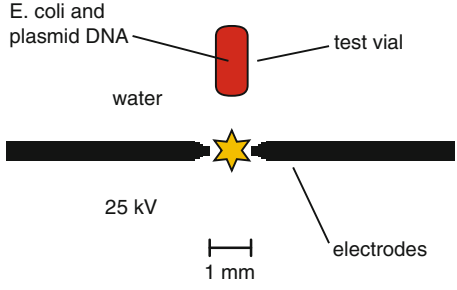


Fig. 7.11 Schematic of an experimental arrangement to transform bacteria using underwater shock waves generated by high-voltage electric discharges. Adapted from Jagadeesh et al. (2004)

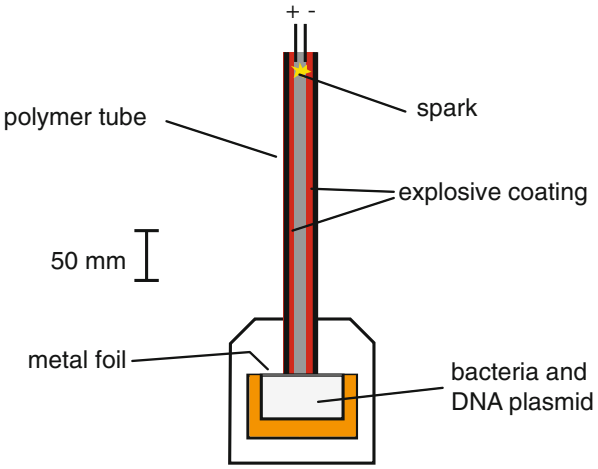


Fig. 7.12 Schematic of a device to transform bacteria by microexplosive shock wave generation. Adapted from Divya Prakash et al. (2011)

aeruginosa and *Salmonella* typhimurium (*S.* typhimurium) could also be transformed with this small device. According to the authors, their transformation method was as efficient as electroporation. Advantages are a better recovery of the cells, reduced cost, and the fact that the methodology is independent of the microorganisms growth phase (Divya Prakash et al. 2011, 2012).

Microbubble collapse is considered the main mechanism responsible for increasing membrane permeability during underwater shock wave exposure of bacteria. As explained in Sect. 4.7, shock wave-induced microjet emission depends on several factors, such as the pressure profile, the properties of the fluid, and the initial bubble size. To demonstrate that acoustic cavitation is the main bacterial transformation mechanism, the transformation efficiency of bacterial suspensions exposed to single-pulse shock waves was compared with that of tandem shock wave-exposed bacteria (Loske et al. 2011, 2012). Three different treatment temperatures (0, 10, and 25 °C) and three delays for tandem shock waves (250, 500, and 750 µs) were tested using an experimental device (Fig. 7.13), based on a *Piezolith 2300* shock wave source (Richard Wolf GmbH). The mean peak-positive pressure recorded at the focus of the shock wave generator with a polyvinylidene fluoride needle hydrophone (Imotec GmbH, Würselen, Germany) at a shock wave generator voltage of 7.5 kV was approximately 38 MPa. In the tandem mode, p^+ of the second shock wave was approximately 18 % smaller than the peak-positive pressure of the first shock wave. Polyethylene vials containing bacterial suspensions were fixed at the focus of the shock wave source an exposed either to 1000 single-pulse shock waves or 500 tandem shock waves (500 pairs of shock waves) at a rate of 0.5 Hz. To confirm bacterial transformation, a plasmid providing GFP expression was transferred to the test vials containing *E. coli* suspensions. The results confirmed that single-pulse shock waves increase the cell membrane permeability, raising the transformation efficiency when compared to the standard $CaCl_2$ method. However, the highest

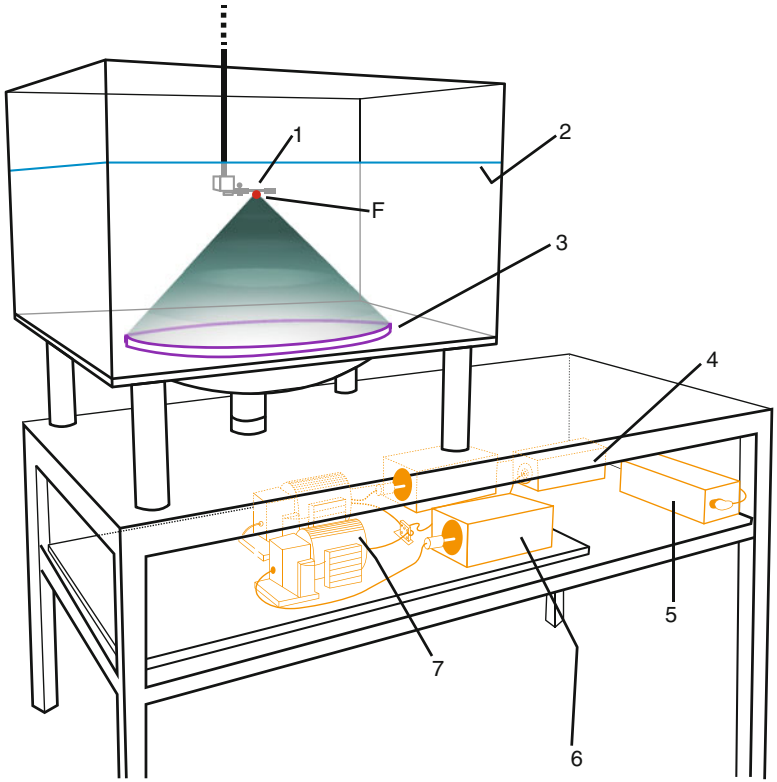


Fig. 7.13 Sketch of a *Piezolith 2300*-based tandem shock wave generator (Richard Wolf GmbH, Knittlingen, Germany), showing (*1*) a sample centered horizontally at the focal spot *F* inside the water tank, (*2*) the water level, (*3*) the piezoelectric shock wave transducer, (*4*) the high-voltage power supply, (*5*) the pulse generator, (*6*) the two spark-gap drivers, and (*7*) the two capacitors

mean transformation efficiency, defined as the number of colony forming units (CFU) divided by the amount (μg) of plasmid DNA, was achieved using tandem shock waves at a delay of 750 μs at 0 °C. This modality increased the number of fluorescent colonies up to 50 times that obtained using standard single-pulse shock waves (Fig. 7.14). The number of viable *E. coli* after tandem shock wave exposure was not significantly dependent on the delay. Further research may help to find the optimal delay for tandem shock wave-transformation.

Transformation efficiency depends on several factors, such as the size of the plasmid and its resistance to shock waves. Maintaining plasmid integrity is important when considering shock wave-mediated transfection. It has been observed that DNA in water solutions may be damaged by shock waves (Kochanski et al. 2001). The relationship between plasmid size and shock wave-mediated bacterial transformation was reported by Campos-Guillén et al. (2012). Plasmids with different sizes (2974, 4742, 7510, 18,200, 20,400, and 22,800 bp) were exposed to single-pulse and tandem shock waves to study the influence of cavitation on the integrity of the plasmids. The plasmids were exposed to 1000 single-pulse shock waves and 500

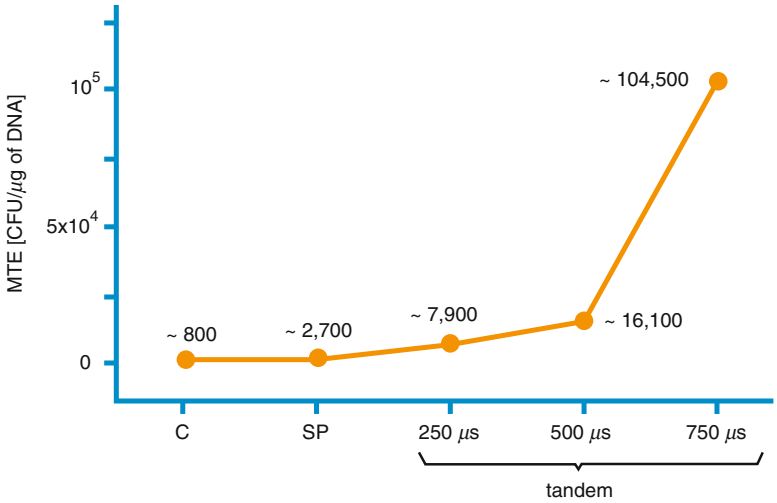


Fig. 7.14 Mean transformation efficiency (MTE), i.e., number of colony forming units (CFU) divided by the amount (μg) of plasmid DNA, of competent *Escherichia coli* after exposure to 1000 single-pulse shock waves (SP) and 500 tandem shock waves at three different delays (250, 500, and 750 μs). The vials in the control group (C) followed the same protocol as treated cells; however, without receiving shock waves. Adapted from Loske et al. (2011)

tandem shock waves (delay = 750 μs) using the piezoelectric shock wave generator, p^+ value, and shock wave rate mentioned above. Plasmid suspensions without shock wave treatment served as controls. The main conclusion of the experiment was that shock wave-mediated transformation using large plasmids is less efficient because large plasmids are ruptured. Shock wave-generated microjets, secondary shock waves, and chemical radicals produced due to bubble collapse inside the test vial could be responsible for the damage of large plasmids. Further research is needed to determine the influence of the shock wave rate, pressure waveform, and dosage on plasmid integrity.

Underwater tandem shock waves at a fixed delay of 750 μs have also been used to replicate a fertility factor-like plasmid (a plasmid responsible for the fusion of two bacterial cells) obtained from a multidrug-resistant *E. coli* strain in a non-pathogenic strain. The results of this study may be helpful in improving methodologies for conjugative plasmid transfer and directly selecting the most interesting plasmids from environmental samples (Soto-Alonso et al. 2015).

7.6 Transformation of Filamentous Fungi

Filamentous fungi are highly versatile microorganisms. Due to their enormous capacity for secretion and metabolic diversity, yeast and fungi are exceptionally useful to produce *recombinant proteins*. Recombinant proteins are made from the

expression of recombinant DNA, that is, DNA that results from the combination of two strands. It is remarkable that recombinant DNA can be created from two different species. Because of this, recombinant DNA is also called *chimeric DNA*. Fungi produce amino acids, antibiotics, insulin, anticoagulants, vaccines, pesticides, biofuels, food preservatives and acidulants, break down dead organic material, and play a crucial role in scientific research, applied sciences, and the industry (Ruiz-Díez 2002; Meyer 2008; Ward 2012; Cruz Hernández et al. 2014; Rivera et al. 2014; van den Berg and Maruthachalam 2015a, b). Since some fungi are pathogenic, genome sequencing is important to enable a better comprehension of their metabolism, allowing the design of strategies to prevent diseases in humans, animals, and plants. Progress in modern genetics relies on the development of efficient, easy-to-use, and cheap transformation methods.

Initial experiments to transform filamentous fungi were reported many years ago (Hinnen et al. 1978; Ballance et al. 1983; Tilburn et al. 1983). More than hundred species have been transformed and a huge amount of scientific articles have been published since then. Genetic transformation of filamentous fungi opened widespread applications to biotechnology. Many industries such as the biopharmaceutical, the enzyme, and the agricultural industry rely on the production of proteins. The total market for industrial enzymes reaches billions of dollars (Demain and Vaishnav 2009). This huge production is only possible with the aid of genetic engineering.

Aspergillus niger (*A. niger*) is one of the most popular fungi for recombinant DNA technology because of its capability to secrete high levels of bioactive proteins and metabolites. This fungus produces more than 1.75 million tons of citric acid annually, as well as many important proteins (Soccol et al. 2006; Lubertozzi and Keasling 2009; Fleissner and Dersch 2010; Ward 2012). *Aspergillus oryzae* (*A. oryzae*) and *Trichoderma reesei* (*T. reesei*) are also important producers of enzymes.

Transgenic fungi are routinely produced by inserting genes from other fungi, bacteria, viruses, and even animals into their genomes; however, the process still presents many challenges. Transformation methods are divided into two categories: biological and physical. Popular biological methods are the production of protoplasts (cells that had their cell wall removed) and AMT (Sect. 7.5) (de Groot et al. 1998; Sánchez et al. 1998; Michielse et al. 2005; Frandsen 2011; van den Berg and Maruthachalam 2015a, b). Protoplast preparation is a difficult process because the enzymes that digest the cell wall of fungi have not been well characterized. A reason for this is that the polymers forming the cell wall are somewhat different for each species. Electroporation, biolistics, vacuum infiltration, and agitation with glass beads are standard physical methods (Rivera et al. 2014; van den Berg and Maruthachalam 2015a). To increase the production levels, new techniques for the efficient introduction of genes into fungi are constantly sought. A thorough overview of all existing transformation methods used for yeasts and fungi can be found in van den Berg and Maruthachalam (2015a, b).

Most conventional methods to transform fungi are inefficient, cumbersome, and have low reproducibility, mainly because the membrane of filamentous fungi has an intricate structure of protein and polysaccharides that hinders its permeabilization

(Lorito et al. 1993; Ozeki et al. 1994; Michielse et al. 2005; Soccol et al. 2006). Furthermore, DNA must enter the nucleus and integrate into the genome.

There are still many potentially useful fungi that are recalcitrant to transformation with standard methods. Shock wave-induced transformation of fungi is a novel and promising methodology that seems to be a solution to these problems (Magaña-Ortíz et al. 2013; Gómez-Lim et al. 2015). As several subjects treated in this book, genetic transformation of fungi with shock waves is an example of the synergy between physics and biology (Castaño 2014; Rivera et al. 2014).

In 2013, underwater shock waves were successfully used to transform fungi for the first time (Magaña-Ortíz et al. 2013). Four important species were chosen for this trial: *A. niger*, *T. reesei*, a fungus employed in the production of cellulases, *Phanerochaete chrysosporium* (*P. chrysosporium*), a fungus that degrades lignin and cellulose, and *Fusarium oxysporum* (*F. oxysporum*), a phytopathogen that causes diseases in crops. Mixtures of spores and DNA were placed inside small polyethylene bags and exposed to shock waves ($p^+ \approx 38$ MPa) at the focus of an experimental *Piezolith 2300* (Richard Wolf GmbH) shock wave source (Sect. 5.4.1). The −6 dB focal volume (Sect. 3.4) of this shock wave source has the shape of a cigar measuring approximately 17 mm in length and 3 mm at the maximum diameter. Each bag contained 5×10^4 and 5×10^3 conidia (asexual, non-motile spores) per milliliter of *A. niger* and the other three species, respectively. The suspension of conidia was mixed with vectors or expression cassettes (50 μg/ml of DNA). Water was used to couple the shock waves into the polyethylene bags containing the conidia suspension. Different numbers of shock waves (between 50 and 400) were tested. The bags were placed horizontally and centered at the focus F of the shock wave source with a holder manufactured specifically for this purpose (Fig. 7.15). As commonly used in AMT protocols, the frequency of transformation was defined as the number of transformants per 10^7 conidia (de Groot et al. 1998). The shock wave treatment reduced the viability of conidia by one order of magnitude; however, the method yielded two to four orders of magnitude more transformed colonies than those reported for AMT or protoplast protocols in all species (de Groot et al. 1998; Meyer et al. 2007). For the four species the achieved transformation frequency was several orders of magnitude higher than that obtained using standard methods. As expected, the efficiency of transformation varied from one fungus to another, because of differences in the composition of the cell walls. The stability of the transformation was confirmed. Figure 7.16 shows micrographs of non-transformed fungi (controls) and shock wave transformed mutants. The presence of *hph* genes was detected in all transformed species by a technique used to amplify DNA, called polymerase chain reaction (PCR). In this first study, shock wave transformation was highly efficient and fast. A main advantage compared with conventional methodologies was that protoplasts were not necessary.

Fungal peroxidases are enzymes required for several industrial applications such as conversion of toxic materials into less harmful substances; however, their production has been limited due to the lack of efficient transformation methods. *P. chrysosporium* plays an important role in a variety of degradation processes. It secretes oxidoreductive enzymes and is considered to be a valuable fungus,

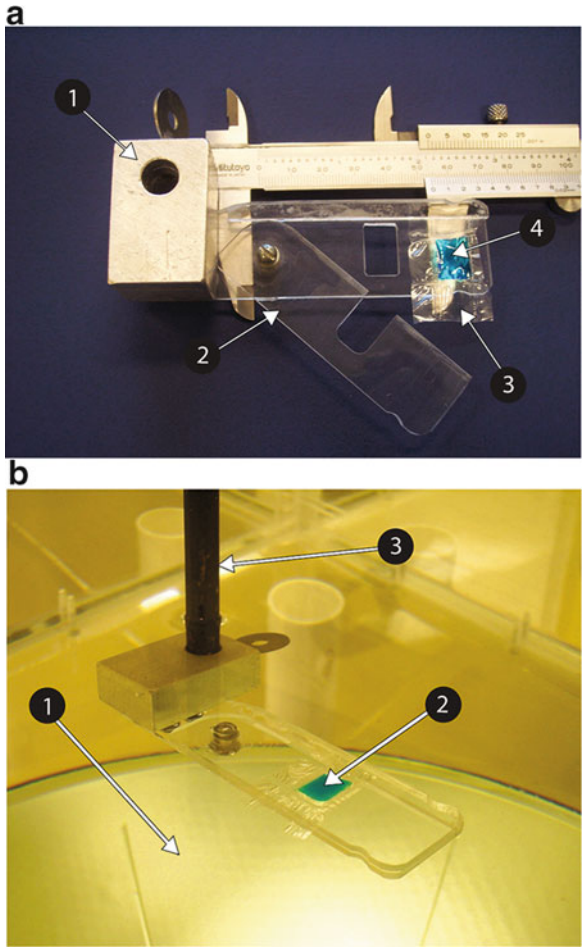


Fig. 7.15 Photographs of a device designed to expose conidia suspensions to shock waves, (**a**) showing the fixing nut (*1*), the Lucite holder (*2*), the heat-sealed polyethylene bag (*3*), and the conidia suspension inside the bag (*4*), before fastening the sample, and (**b**) showing the piezoelectric shock wave transducer (*1*), the conidia suspension (*2*), and the support of the xyz positioner (*3*), during shock wave exposure. The color (*eBook*) of the suspension was altered for clarity. (Photograph: F. Fernández)

because, as mentioned above, it degrades lignin and cellulose, which are difficult-to-degrade polymers. Coconi-Linares et al. (2014) used the same shock wave source and energy settings previously described to significantly increase the expression of the mitochondrial-nucleoid protein (MnP1) and the lignin peroxidase isozyme H8 (LiPH8) from *P. chrysosporium*. A high peroxidase activity was observed in the recombinant strains but not in the wild-type strain. In order to study whether the co-expression of laccases (enzymes used for many industrial applications, such as textile dyeing and bioremediation) and peroxidase in *P. chrysosporium* improves the degradation of phenolic and non-phenolic substrates or not, Coconi-Linares et al. (2015) tested the constitutive co-expression of the *lacIIIb* gene from the fungus *Trametes versicolor* and the *vpl2* gene from the fungus *Pleurotus eryngii*, as well as the endogenous genes *mnp1* and *lipH8* by shock wave-induced genetic transformation, using a similar shock wave source (*Piezolith 2501*, Richard Wolf GmbH) and parameters as mentioned above. Their results revealed that the co-overexpression of

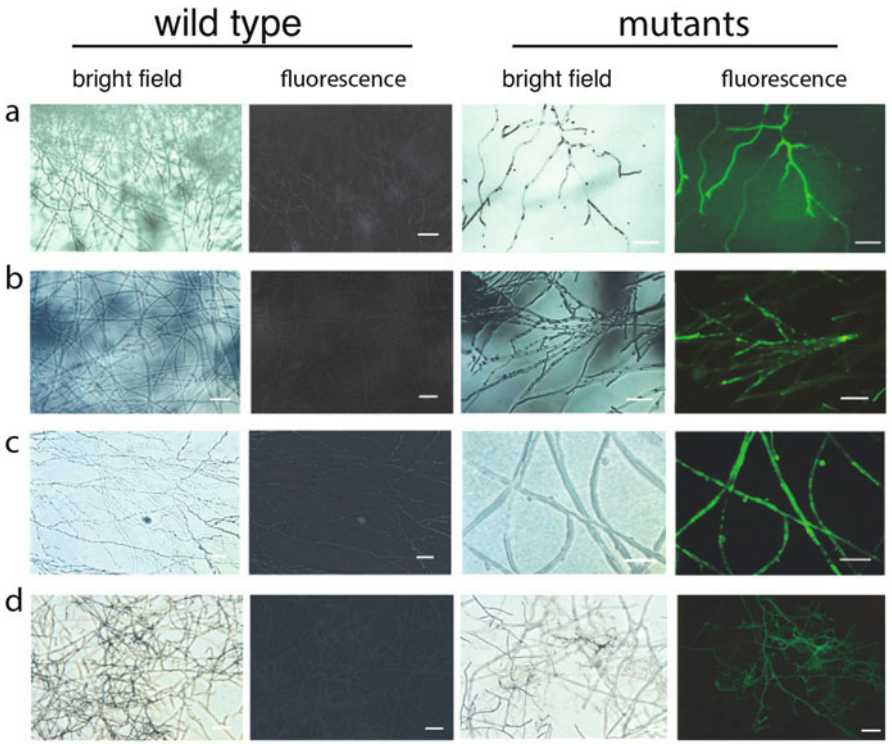


Fig. 7.16 Bright field and fluorescence micrographs of 3-day-old cultures of non-shock wave-exposed (wild type) and shock wave-transformed mutants of (**a**) *Aspergillus niger*, (**b**) *Fusarium oxysporum*, (**c**) *Trichoderma reesei*, and (**d**) *Phanerochaete chrysosporium*. Fluorescence is only observed in mutants (green color in the *eBook*). (Scale bar: 10 μm)

peroxidases and laccases was enhanced up to five-fold as compared with the wild type (control). The authors concluded that the tested enzymes can be constitutively expressed in a single transformant of *P. chrysosporium* in minimal media.

In another study (Escobar-Tovar et al. 2015), the pathogenic fungus *Mycosphaerella fijiensis* (*M. fijiensis*), responsible for the black leaf streak disease (also called black Sigatoka) that causes significant losses in production of bananas and plantains, was genetically transformed with 150 single-pulse shock waves ($p^+ \approx 38$ MPa) generated inside the water tank of the experimental piezoelectric shock wave source mentioned in the previous paragraphs. This fungus has been notoriously recalcitrant to transformation by conventional methods. The genetic stability of the transformed fungi was verified for more than ten generations. Antibiotic (*hygromycin*) resistant colonies with GFP activity were produced. Successful genetic transformation was confirmed by PCR and Southern blot, a method for detection of a specific DNA sequence. The shock wave method generated approximately 12,000 transformants per 10^6 conidia, compared to 80–160 transformants per 10^6 spheroplasts (cells from which their wall has been partially removed) commonly

obtained using time-consuming standard techniques (Balint-Kurti et al. 2001; Portal et al. 2012). These results indicate that shock wave-induced transformation of *M. fijiensis* could help to develop efficient alternatives to fungicides used to control black Sigatoka, which represent a risk for humans and the ecosystem.

The details of the mechanisms responsible for shock wave-mediated fungal transformation are not fully understood yet; however, it is believed that acoustic cavitation produced as shock waves propagate through the suspensions containing plasmid and conidia is the main cell membrane permeabilization mechanism. This was confirmed by showing that tandem shock waves (Sect. 4.7) significantly improve DNA delivery into filamentous fungi, compared to single-pulse shock waves (Loske et al. 2014). The experimental piezoelectric tandem shock wave generator used for this purpose was similar to the one mentioned above (Fig. 7.13); however, in this case a *Piezolith 2501* (Richard Wolf GmbH) shock wave source was used. Genetic transformation of *A. niger* was assessed with a plasmid that conferred resistance to an antibiotic and contained the GFP reporter gene. Polyethylene bags with fungal suspension (Fig. 7.15) exposed to 100 single-pulse shock waves were compared to samples that received 50 tandem shock waves at different delays (200, 300, 400, and 500 μs). Using tandem shock waves at a delay of 300 μs approximately 84 % more transformants were obtained than those using standard single-pulse shock waves. At this delay, the number of transformants was 420 times higher than those obtained using protoplasts, 170 times higher than using electroporation, and 8200 times higher than using AMT (Ozeki et al. 1994; Meyer et al. 2007; de Groot et al. 1998). Since tandem shock waves enhance bubble collapse, these results indicate that acoustic cavitation is the main transformation mechanism. According to the numerical simulations (Canseco et al. 2011), tandem shock waves enhance bubble collapse at a delay between 270 and 285 μs. These values are surprisingly close to the 300 μs-delay that enhanced transformation efficiency of *A. niger*.

7.7 Bactericidal and Fungicidal Effects of Shock Waves

The destructive effects of ultrasound on microorganisms (Davies 1959) were known long before Gilliland and Speck (1967) reported that the action of non-focused shock waves on *E. coli* was not an important cause of bacterial death. The study of shock wave-induced bacterial inactivation was resumed after the clinical introduction of SWL in 1980.

Several authors reported that, despite of initial sterile urine cultures, viable bacteria were detected after SWL. In some cases, bacteriuria (presence of bacteria in urine), bacteremia (presence of bacteria in blood), and urosepsis (infection that spreads into the bloodstream) were observed during or after SWL of renal calculi (Zink et al. 1988; Müller-Mattheis et al. 1991; Silber et al. 1991; Raz et al. 1994; Yilmaz et al. 2003). As mentioned in Chap. 5, SWL is contraindicated in patients having an acute bacterial infection because bacteria could enter the bloodstream through damaged vessels. Shock wave-induced cavitation (Sect. 4.7), free radical

production, and streaming may destroy bacteria and release large amounts of protein into the blood stream, causing septic shock. Infection is also a contraindication for the use of shock waves in orthopedics (Chap. 6).

There are many studies describing the interaction of underwater shock waves with bacteria; however, results are controversial. Different pressure waveforms and experimental conditions, such as the material and the shape of the vials used (Cleveland et al. 1997), the size of the cell suspension relative to the pressure field (Dietz-Laursonn et al. 2016), and the type and concentration of the suspension and the temperature, may be responsible for the discrepancies. Elbers and colleagues (1988) observed no significant effect on calculogenic bacteria after in vitro treatment with 2400 shock waves generated with an *HM3* lithotripter (Dornier MedTech GmbH) operated at up to 24 kV. The impact of 1000 extracorporeal shock waves generated with an electrohydraulic lithotripter at 18 kV on the microbiological flora of staghorn calculi was analyzed in vitro by Stoller and Workman (1990). Their conclusion was that SWL had no evident bactericidal effect on infected staghorn calculi. Ohshima et al. (1991) reported that *E. coli* JM 109/pKPDH2 is difficult to inactivate by shock waves produced with a shock tube. The relatively low peak-positive pressure used ($p^+ \approx 0.1$ MPa) could be the main reason for this result. Nevertheless, the authors observed that bacteria could be killed when small bubbles were introduced into the cell suspension, indicating that acoustic cavitation is a bactericidal mechanism. Kerfoot et al. (1992) studied the inactivation of *Pseudomonas aeruginosa, Streptococcus faecalis, Staphylococcus aureus* (*S. aureus*), and *E. coli* with shock waves. Aliquots of bacterial suspensions of each of the four strains received up to 4000 shock waves generated at 20 kV and a rate of 100 shock waves per minute with an *HM3* lithotripter (Dornier MedTech GmbH). The experiment was repeated with a *Piezolith 2200* piezoelectric lithotripter (Richard Wolf GmbH) using the same number of shock waves produced at an energy level 4 and a rate of 2 Hz. The main conclusion of the study was that shock waves do not possess a significant bactericidal activity.

After SWL, small residual fragments may remain in the renal collecting system for months. These fragments often contain bacteria that cause persistent bacteriuria. Michaels and colleagues (1988) investigated prospectively the incidence of persistent *Proteus mirabilis* (*P. mirabilis*) bacteriuria after SWL in women with *P. mirabilis* urinary tract infections and struvite calculi. All patients underwent SWL with an *HM3* electrohydraulic lithotripter (Dornier MedTech GmbH). No treatment exceeded 2000 shock waves generated at 24 kV. The authors concluded that in contrast to intact infected renal calculi, residual stone fragments after SWL often are susceptible to sterilization with antimicrobials. Another prospective study in 135 patients with renal or upper ureteral stones associated with persistent urinary tract infection was published by Pode et al. (1988). SWL treatments were performed on an *HM3* lithotripter. The analysis revealed a correlation between the incidence of residual macroscopic stone fragments and the presence of persistent infection.

In vitro studies on the bactericidal effect of shock waves on *S. aureus* were reported by von Eiff et al. (2000). Suspensions containing bacteria were exposed to shock waves using an experimental *XL1* lithotripter (Dornier MedTech GmbH) at

energy levels that are standard for clinical SWL. The authors concluded that shock waves as used in clinical applications have bactericidal effects on *S. aureus* and could be an alternative in cases of difficult-to-cure-infections.

Gollwitzer and coworkers (2004) found a significant bactericidal effect of shock waves for both Gram-positive (*Staphylococcus epidermidis* and *Enterococcus faecium*) and Gram-negative bacteria (*Pseudomonas aeruginosa*). The effects of shock waves on the cell wall integrity of *S. aureus* were studied by Horn et al. (2009). Bacterial suspensions were exposed up to 12,000 shock waves (EFD between 0.38 and 0.96 mJ/mm^2). Suspensions of *S. aureus* permeabilized with isopropanol were used as positive controls. The fluorescence of the shock wave-treated, permeabilized, and untreated bacteria was measured and compared. As expected, shock waves showed a significant energy-dependent antibacterial effect; however, only high energies and large numbers of shock waves resulted in a significant increase in fluorescence compared with the untreated control. The fluorescence of these bacteria was still much less than that of the positive control. Because of this, the authors concluded that not only membrane permeabilization, but also intracellular effects might be involved in shock wave-induced inactivation of *S. aureus*.

Gerdesmeyer et al. (2005) also evaluated the effect of lithotripter shock waves on *S. aureus* in vitro as a function of the EFD and the number of shock waves. At least 2000 shock waves with an EFD of 0.96 mJ/mm^2 were needed to inactivate bacteria. The bacterial viability was reduced significantly by further increasing the number of shock waves. They also reported that a threshold EFD of approximately 0.6 mJ/mm^2 was necessary to achieve an antibacterial effect. Bacterial inactivation increased exponentially by increasing the EFD above this threshold.

Because bacteria may remain active inside kidney stones (McAleer et al. 2003) and massive endotoxin release could occur with infection stone manipulation, Quintero et al. (2008) studied the influence of shock waves on the viability of bacteria contained inside kidney stone phantoms. *S.* typhimurium infected stone phantoms were manufactured and exposed in vitro to shock waves in an electrohydraulic lithotripter ($p^+ \approx 30$ MPa). Another set of infected stones was pulverized using the same number of shock waves in a piezoelectric extracorporeal lithotripter ($p^+ \approx 38.5$ MPa). With the electrohydraulic lithotripter about 95 % of the microorganisms were inactivated after 400 shock waves; however, the effect was associated mainly with the ultraviolet radiation and the visible light generated at the *F1* focus of the shock wave source. After approximately 2700 shock waves to stones protected from the spark-gap radiation by a black polypropylene bag, about 29 % and 14 % of all bacteria were inactivated with the piezoelectric and the electrohydraulic lithotripter, respectively. The main conclusion of this study was that shock waves should not be considered as an efficient bacterial inactivation mechanism during SWL. In an evaluation of the incidence of persistent bacteriuria among patients with infected stones who were treated by SWL versus those treated by percutaneous nephrolithotomy (PCNL), Riad and colleagues (2008) found that PCNL is better than shock wave monotherapy to eradicate bacteriuria; however, SWL showed good outcomes for infection clearance for small infected stones in the renal pelvis.

Independently of the interaction of shock waves with bacteria during SWL, chronic bacterial prostatitis could be an ESWT indication once the antibacterial effects of shock waves at therapeutic energy flux densities and shock wave numbers are confirmed for uropathogenous microorganisms (Zimmermann 2013).

A non-clinical application of shock waves to inactivate bacteria is their potential use in the food industry. Non-thermal food preservation methods that preserve nutriments, flavor, color, and taste, while inactivating non-desired microorganisms, are constantly sought. Several techniques such as hydrostatic pressure, pulsed electric fields, gamma irradiation, and thermo-sonication have been tested (Barbosa-Cánovas et al. 2000; Marx et al. 2011); however, their industrial application is still limited. Shock wave exposure as a possible method for food preservation has been analyzed in the past (Loske et al. 1999; Alvarez and Loske 2010). *E. coli* were exposed to underwater shock waves ($p^+ \approx 44$ MPa) generated with an electrohydraulic shock wave generator. Contrary to standard electrohydraulic shock wave sources, a stainless steel parabolic (focal distance = 20 mm) instead of an ellipsoidal reflector was used to produce a plane shock front. A total of 28 polypropylene transfer pipettes were filled with *E. coli* suspension, heat sealed, and placed on a plane Lucite rack (Fig. 7.17) at approximately 123 mm from the focus of the parabolic reflector (Fig. 7.18). The experiment was repeated several times and each time a

Fig. 7.17 Photograph of a Lucite rack designed to fasten many polypropylene vials filled with bacterial suspensions for exposure inside an electrohydraulic shock wave source equipped with a parabolic reflector. (Photograph: A. Sánchez)

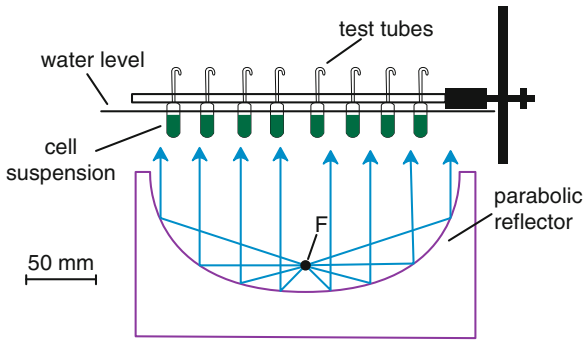


Fig. 7.18 Schematic of an electrohydraulic shock wave source with a parabolic stainless steel reflector to expose a set of vials containing microorganisms to plane shock waves

total of 2000 shock waves were applied to the rack at a rate of 0.4 Hz. Every 500 shock waves, four test tubes were randomly taken out of the shock wave generator and analyzed. The same protocol was applied to non-shock wave-exposed control samples. The amount of surviving bacteria was determined by the total viable count (TVC) method, which gives a quantitative estimate of the number of bacteria, yeast, or fungi in a test sample. Biochemical analyses did not reveal changes in the metabolism of the microorganisms. Approximately 570 shock waves were needed to reduce the initial amount of microorganisms by 90 %. The reduction seemed to follow an exponential behavior. Shock wave-induced microjet emissions, production of free radicals, as well as shearing forces, were believed to be responsible for the observed bactericidal effect.

Further analyses, exposing suspensions of *E. coli*, *S.* typhimurium, and *Listeria monocytogenes* (*L. monocytogenes*) to shock waves generated by an open water bath electrohydraulic shock wave source, revealed that the bactericidal effect was primarily produced by a synergy between the shock wave pressure, the pulse of light coming from the spark-gap at *F1*, and the shock wave generated cavitation (Loske et al. 2002a; Alvarez et al. 2004). *L. monocytogenes* turned out to be the most susceptible bacterium. The resistance of *S. typhimurium* was similar to that of a non-pathogenic strain of *E. coli.* An interesting finding was that a pathogenic *E. coli* strain (O157:H7) behaved differently than the non-pathogenic strain (ATCC 10536). *E. coli* O157:H7 inactivation depended on its phase of growth and not on the shock wave dosage, while the response of *E. coli* 10536 was the opposite. These studies were performed exposing suspensions of microorganisms to shock waves focused with an ellipsoidal reflector (Fig. 7.19). The results revealed that higher shock wave doses and data obtained from a range of foods and a variety of microorganisms are needed before shock wave inactivation of bacteria could be attractive to the food industry. Exposure of microorganisms to tandem shock waves (Sect. 4.7) is an interesting alternative.

In vitro experiments exposing *L. monocytogenes* and *E. coli* O157:H7 to the action of different doses of shock waves inside a piezoelectric shock wave source

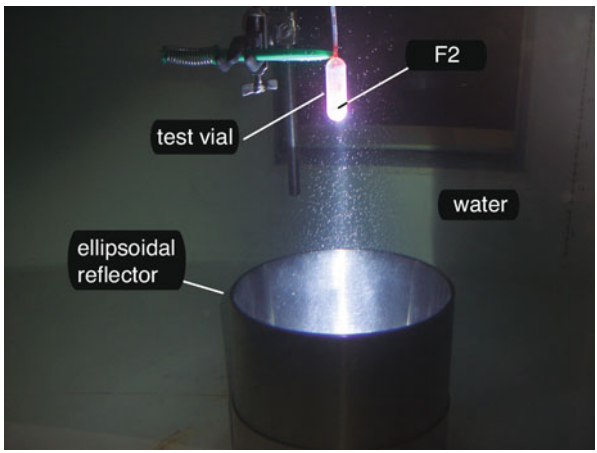


Fig. 7.19 Photograph showing a vial containing bacterial suspension, during shock wave exposure at the focus *F2* of an electrohydraulic shock wave source. The photograph was taken at the instant of the underwater electric discharge at *F1*. Small bubbles can be seen in the water along the shock wave path. (Photograph: F. Fernández)

modified to generate either standard (single-pulse) or tandem shock waves (Sects. 4.7 and 5.4.1) showed that *L. monocytogenes* was more resistant to tandem shock waves than the pathogen *E. coli* strain (Alvarez et al. 2008). In both cases, the use of tandem shock waves significantly enhanced bacterial inactivation. *E. coli* and *L. monocytogenes* were not inactivated after applying 6800 single-pulse shock waves ($p^+ \approx 38$ MPa) at a rate of 0.7 Hz; however, exposing *L. monocytogenes* to 3400 tandem shock waves at a delay of 900 µs, inactivated approximately 37 % of the initial amount of bacteria. Using the same tandem shock wave dose at the same delay inactivated about 51 % of the *E. coli* population. These results reveal that cavitation is responsible for shock wave-induced bacterial inactivation and that the effect can be improved by enhancing acoustic cavitation.

In vitro application of clinical doses of shock waves on *Candida albicans planktonic* cells by Petrou and colleagues (2009) revealed that a cell death of up to 90 % can be achieved by applying 4000 shock waves at a rate of 3 Hz. This is of clinical importance not only in urology but also in dentistry (Sect. 7.8), because *C. albicans* is a fungus that forms biofilms at the site of infections, preventing the immune system to act. Biofilms may release bacteria causing chronic infections. A promising use of shock waves is based on the fact that there is convincing evidence that pressure pulses can damage bacterial biofilm. A high percentage of all infections initiate from biofilms, i.e., microorganisms embedded within a matrix of polymeric substance, composed of proteins and polysaccharides. Biofilms can form on living and non-living surfaces, such as human tissue, intrauterine devices, catheters, and prosthetic joints. For instance, *Staphylococci* form biofilms on injured tissues and medical implants. The resulting infections are difficult to treat, because antibiotics fail to penetrate the biofilms. Initially bacteria may adhere to a surface through van der Waals forces, i.e., weak electric forces that attract neutral molecules to one another; however, strong cell adhesion structures are developed if the cells are not removed in a short period of time.

Wanner et al. (2011) studied the potential of 500 pressure pulses (EFD = 0.16 mJ/mm^2) to enhance the penetration of antimicrobial agents into strains of *S. aureus* and *Staphylococcus epidermidis* biofilms in vitro. Their results revealed that the biofilm layers were damaged by the pressure pulses, facilitating the penetration and action of the antibiotics. Divya Prakash et al. (2015) reported the disruption of biofilms both in vitro and in vivo. A small microexplosive shock wave generator, similar to the one described in Sect. 7.2, was used in vitro to disrupt biofilms grown on urinary catheters (Divya Prakash et al. 2011; Jagadeesh et al. 2011; Rakesh et al. 2012). Shock waves of about 1.25 J were produced at the open end of the device. When the biofilms were treated with ciprofloxacin, no reduction in the number of bacteria was observed, whereas ciprofloxacin treatment together with the action of a single shock wave significantly reduced the TVC and the number of bacteria observed on scanning electron microscopy (SEM). Even if the shock wave alone did not have a significant antibacterial effect, the authors hypothesized that the shock wave action ruptured the polysaccharide matrix surrounding the biofilm, liberating bacteria and increasing the efficiency of the antibiotic. The study included Gram-positive (*S. aureus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *S.* typhimurium).

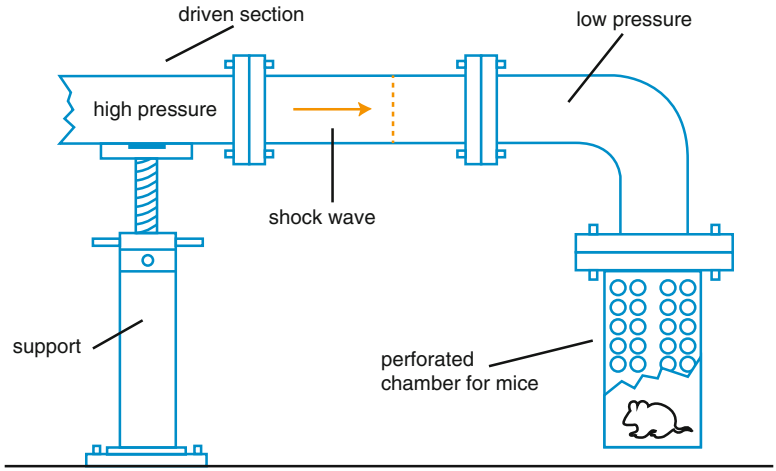


Fig. 7.20 Modified version of the diaphragmless shock tube developed by Hariharan et al. (2011) for in vivo low-energy shock wave exposure of mice

In vivo trials have been performed in mice previously infected intranasally with *P. aeruginosa*, exposed to shock waves emitted by a modified version of the diaphragmless shock tube described by Hariharan et al. (2011). A first group of animals was treated for three days with ciprofloxacin alone, a second group was subjected only to the action of a single shock wave, and a third group received one shock wave followed by the ciprofloxacin treatment. Mice in groups two and three were subjected to one shock wave ($p^+ \approx 48$ MPa) while being housed in a chamber that was coupled with an L-shaped bend to the end of the shock tube (Fig. 7.20). All mice in groups two and three survived, demonstrating that the diaphragmless shock tube can be used to study the effects of shock waves on lung tissue in this animal model. The animals were killed three days after treatment and the effect on lung tissue was examined. On SEM images it was observed that the infected mice developed biofilms in the lung after three days. In the first group there was no decrease in the bacterial counts in homogenized lung samples, but this bacterial burden was significantly decreased in animals that received antibiotic treatment combined with shock wave therapy. The authors also used their shock tube to study the effects on an *S. aureus* skin suture infection model in mice. In all mice carrying infected sutures that were subject to both antibiotic and shock wave therapy, the degree of infection was reduced significantly. Using only one shock wave to disrupt biofilms and enhance the efficiency of antibiotics is a novel approach.

The antibacterial effect of underwater shock waves has also been studied to solve problems very different from clinical applications. An interesting example is ship ballast water sterilization. Ship ballast water is a worldwide problem that has not been solved adequately. Aquatic plant and animal species from remote regions are discharged with ballast water from vessels and may modify or destroy local marine

ecosystems. The bactericidal effects of free radical production and secondary shock wave emission after shock wave-induced bubble collapse have been proposed to sterilize water. Abe et al. (2007) studied the possibility to inactivate a marine *Vibrio* sp. in a suspension with a single shock wave generated by a gas gun. *Vibrio* sp. is a Gram-negative bacterium found in saltwater. Bacterial inactivation was evaluated by plate counting of viable cells. Complete cell inactivation was achieved at a peak-positive pressure of approximately 200 MPa. Tsujii et al. (2012) used an electrohydraulic shock wave source to study shock wave inactivation of marine *Vibrio* sp. Even if the goal of the study was the inactivation of microorganisms contained in ship ballast water, their experimental arrangement was similar to experiments performed for biomedical applications. In one part of the experiment, a 5-mm-width air gap between the discharge chamber and the cell suspension prevented shock waves from propagating into the cell suspension and only the electromagnetic radiation produced by the underwater high-voltage discharge reached the microorganisms. The discharge rate was fixed at 0.25 Hz and the cell viability was estimated by using the plate counting method. By blocking the shock waves, the number of CFU/ml decreased about 30 % from 100 to 200 electric discharges. Comparing the same numbers of generated discharges, a reduction of approximately 98 % in the number of CFU/ml was observed when cells were exposed to both the radiation and the shock waves. Even if the experimental conditions were different and the peak-positive pressure was much lower (approximately 4.5 MPa) the conclusions of these experiments coincide with previously published results (Loske et al. 1999; Alvarez et al. 2004).

7.8 ESWT in Dentistry

Several experimental studies and clinical trials reveal that the use of shock waves in dentistry may have potential in the removal of tooth biofilm, the regeneration of alveolar bone, the eradication of periodontal pathogens, and the reduction of tooth mobility after active orthodontic movement.

Elimination of bacterial biofilm and concrements on the root surface of teeth is crucial to treat *periodontitis*, i.e., an inflammatory disease affecting the tissues that surround the teeth. Standard techniques are plaque and calculus removal, using curettes and ultrasound. A study to assess the potential of shock waves to remove calculus and biofilms on extracted human teeth in vitro by Müller and coworkers (2011) revealed an inefficient calculus removal from the root surface. However, shock waves were able to eliminate bacterial biofilms from infected surfaces to a degree comparable with ultrasound. These results are relevant, because an in vitro biofilm model, which consisted of six species representative for supragingival plaque, was used. To evaluate in vitro calculus removal, a first group included ten randomly selected teeth that were treated with a *Duolith* shock wave source (Storz Medical AG) at a distance of 4 mm. The teeth were exposed to shock waves (EFD = 0.4 mJ/mm^2) at a rate of 3 Hz during 1 min in Petri dishes containing 20 ml

sterile saline. The saline solution acted as coupling fluid. In a second group, ten teeth were treated with a conventional ultrasonic device at medium power setting. Biofilms were grown in 24-well polystyrene cell culture plates on 18 hydroxyapatite discs. The thickness of the biofilms ranged between 30 and 40 µm. All discs were removed from the wells, immersed in Petri dishes containing physiological saline and divided into three groups. Discs in the positive control group ($n=6$) stayed untreated. In group two, six discs were exposed to shock waves at the EFD, rate, and duration mentioned above, and in the last group, six discs were treated with ultrasound. ESWT could have a promising future in the treatment of periodontitis if the bactericidal effect of shock waves is not significantly reduced under clinical situations where bacteria are covered by gingival tissues.

A few years before the above mentioned study, Novak et al. (2008) determined the antibacterial effect of shock waves on oral bacteria by exposing bacterial suspensions of six species to shock waves (EFD up to 0.3 mJ/ mm^2) with a *DermaGold* (MTS Europe GmbH, Konstanz, Germany) shock wave source. Their results revealed that 100 shock waves significantly reduced the viability of *Streptococcus mutans* and an unencapsulated strain of *Porphyromonas gingivalis*. No bactericidal effect could be achieved with up to 500 shock waves to *Fusobacterium nucleatum*, *Actinomyces naeslundii*, *S. aureus*, and an encapsulated *Porphyromonas gingivalis* strain.

More recently, Steinke and Rädel (2014) successfully treated patients suffering from therapy resistant *gingival pockets* (abnormal depth of the space between a tooth and the surrounding gingival tissue, caused by periodontitis) with and without bone resorption using electromagnetically generated shock waves. Shock waves were coupled through the cheek or lip into the periodontal area to be treated. In order to target the painful zone, the hand-piece of the shock wave generator was held by the patient. Treatments were performed without anesthesia. A total of 1000 shock waves (EFD=0.23 mJ/mm^2) were applied to each area at a rate of 4 Hz using a *Duolith* (Storz Medical AG). Each patient received four treatments at a one-week interval to reduce the size of the pockets and induce the formation of alveolar bone. Results were documented radiographically, by visual assessment of the insufficient periodontal area, and by measurement of the pocket depth. In all four cases, both the pocket size and the tooth mobility were reduced; however, bone recovery was successful in two cases only. The authors concluded that ESWT represents a potential method to induce endogenous bone augmentation and/or to improve bone quality.

To prove the hypothesis that shock waves promote the regeneration of alveolar bone following *Porphyromonas gingivalis*-induced periodontitis in rats, Sathishkumar and coworkers (2008) infected rats with *P. gingivalis* for 10 weeks, causing alveolar bone resorption. Part of the rats were exposed to a single shock wave therapy of 100, 300, or 1000 shock waves (EFD=0.1 mJ/mm^2) on both cheeks using a *DermaGold* shock wave generator (MTS Europe GmbH). The alveolar bone levels determined at 0, 3, 6, and 12 weeks after ESWT were compared with those of untreated control rats. The alveolar bone levels of the rats treated with 300 and 1000 shock waves significantly improved compared with the levels of the sham group, indicating that ESWT could be an adjunct in the regeneration of periodontal tissue after periodontal disease.

Since shock waves have a bactericidal effect on bacterial strains of bone-associated infections (Gollwitzer et al. 2004) and may induce alveolar bone regeneration (Sathishkumar et al. 2008), ESWT has been proposed as a treatment for *peri-implantitis*, i.e., the destructive inflammatory process of tissues surrounding osseointegrated implants (Li et al. 2010).

Shock wave-induced reduction of tooth mobility (TM) and the rehabilitation of adjacent tissues have been studied in vivo. TM is increased after active orthodontic treatment. A complete rehabilitation of the dentoalveolar apparatus takes more than one year. It is evaluated manually and digitally by exerting force to the tooth. Hazan-Molina et al. (2012) found that the application of shock waves during orthodontic tooth movement may alternate the periodontal remodeling expected rate. In their report, they concluded that shock waves influence the expression of the vascular endothelial growth factor (VEGF) and certain cytokines, which play a central role in the regulation of responses to infections.

Another study on the effect of ESWT on TM after orthodontic alignment of the teeth was reported by Falkensammer et al. (2015). Patients who had undergone orthodontic treatment with fixed appliances were exposed to 1000 focused shock waves (EFD between 0.19 and 0.23 mJ/mm^2; shock wave rate = 5 Hz) with an *OrthoGold 100* shock wave source (MTS Medical UG) after receiving topical anesthesia in the vestibular mucosa, between the lower right and left canine. Shock wave coupling was assured by applying sonic gel between the chin and the lower lip. Patients in the control group were treated with an acoustic sham. On the day of bracket removal, the pocket depths around the teeth and bleeding on probing (BOP) were evaluated. This was repeated six months later. After shock wave or sham treatment, the Periotest, a method to evaluate TM and damping characteristics of the periodontium (tissue that surrounds and supports the teeth) by measuring the reaction to a reproducible impact applied to the tooth crown (Schulte and Lukas 1992; Goellner et al. 2013), was done two times for each tooth. Manual testing and classification followed. The authors concluded that the mobility values for the shock wave-treated patients decreased more rapidly than those of the sham group. Furthermore, in the placebo group the BOP decreased from 30 % to 28 % and in the ESWT group from 29 % to 14 %. The bactericidal potential of ESWT could help to additionally improve periodontal tissue regeneration, nevertheless, ESWT is still far from a routine clinical use, because treatment protocols are not clear and the cellular mechanisms involved are not understood.

Falkensammer et al. (2014) reported the results of a randomized, placebo-controlled clinical trial to study the possible effect of noninvasive shock waves on the stability of temporary anchorage devices (TADs) under orthodontic loading. Thirty adult patients with mesially directed orthodontic movement of the mandibular second molar into the extraction site of the mandibular first molar were enrolled. The fixed orthodontic devices included active coil springs and TADs in the mandibular alveolar bone. Patients in the treatment group received topical anesthesia and were exposed to 1000 pressure pulses (EFD between 0.19 and 0.23 mJ/mm^2) at a rate of 5 Hz using an *OrthoGold 100* (MTS Medical UG) device, after applying sonic gel on the cheek as a coupling medium. Patients in the sham group were

treated with a device that produces a similar noise as real *OrthoGold 100* but does not generate pressure pulses. The TADs positions were measured at the day of placement and four months later. An in vitro model was used to confirm the reliability of the impression process of the TADs. The results of the study revealed that, at the above mentioned dose, one treatment does not improve the stability of the TADs during orthodontic loading.

Periodontal ligament fibroblasts (PDLF) may express pro-inflammatory molecules, participating in development of periodontal diseases when stimulated by biological promoters like lipopolysaccharide (LPS). They can also liberate inflammatory cytokines when mechanical stimuli are applied during orthodontic treatment. To study if shock waves also could induce the inflammatory reaction of PDLF, Cai et al. (2016) applied shock waves generated at 3 Hz by a *DermaGold 100* (MTS Europe GmbH) unfocused electrohydraulic shock wave generator on human periodontal ligament fibroblasts (hPDLF). A water bath setup at 37 °C was connected to an *OP155* applicator to couple the shock wave energy into polypropylene tubes containing cell suspension. The distance between the shock wave applicator and the cell suspension was maintained fixed at 40 mm. Three different energy densities (0.05, 0.10, and 0.19 mJ/mm^2) and numbers of shock waves (100, 300, and 500) were tested. After shock wave exposure, the hPDLF were reseeded on 24-well plates. The results showed no significant difference in cell viability and proliferation between treated groups and the control group, as well as among groups receiving shock wave treatment with different EFD and number of shock waves. The authors concluded that no negative effects on cell viability/proliferation were observed after exposing hPDLF up to 500 shock waves at an EFD of 0.19 mJ/mm^2. This type of study is valuable to determine shock wave treatment parameters for clinical application of ESWT in dentistry.

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