

ISMST



News letter

APRIL, 2006
VOLUME 2, ISSUE 1

Chief Editor

• **Paulo Roberto Dias dos Santos, MD** (Brazil) - prds@uol.com.br

Associate Editor

• **Ching-Jen Wang, MD** (Taiwan) w281211@adm.cgmh.org.tw

Editorial Board

- **Ana Claudia Souza, MD** (Brazil) anaclaudia@cortrel.com.br
- **Carlos Leal, MD** (Columbia) leal@owc.com.co
- **Heinz Kuderna, MD** (Austria) kuderna-unfallchir.wien@aon.at
- **Kimberly Eickmeier, MD** (USA) Keickmeier@christieclinic.com
- **Leonardo Jaime Guiloff Waissbluth, MD** (Chile) - lguiloff@davila.ch
- **Lowel Weil Jr, MD** (USA) lweiljr@weil4feet.com
- **Ludger Gerdsmeyer, MD** (Germany) gerdsmeyer@aol.com
- **Matthias Buch, MD** (Germany) matthiasbuch@aol.com
- **Paulo Roberto Rockett, MD** (Brazil) rockett@terra.com.br
- **Richard Levitt, MD** (USA) falevitt@aol.com
- **Richard Thiele, MD** (Germany) harthi@t-online.de
- **Robert Gordon, MD** (Canada) dracula65@hotmail.com
- **Sergio Russo, MD** (Italy) serghiey@hotmail.com
- **Vinzenz Auersperg, MD** (Austria) Vinzenz.Auersperg@akh.linz.at
- **Wolfgang Schaden, MD** (Austria) med.eswt.schaden@aon.at

Veterinary Committee

- **Scott Mc Clure, DVM** (USA) mcclures@iastate.edu
- **Ana Liz Garcia Alves, DVM** (Brazil) anaalves@fmvz.unesp.br
- **Ana Cristina Bassit, DVM** (Brazil) anafbassit@uol.com.br

Editorial Office

Avenida Pacaembu, 1024
CEP 01234-000 - São Paulo - Brazil
Fone: 55-11-3825-8699
E mail: prds@uol.com.br

website: www.ismst.com



Editorial · Editorial comments

Ching-Jen Wang, M.D.

Clinical professor
Chang Gung University School of Medicine
Chang Gung Memorial Hospital - Kaohsiung
Medical Center · Kaohsiung, Taiwan.

Extracorporeal shockwaves in musculoskeletal system (Orthotripsy) is gaining fast and steady recognition worldwide because of consistent and good clinical results either with controlled or non-controlled studies on proximal plantar fasciitis of the heel, lateral epicondylitis of the elbow, calcifying tendonitis of the shoulder and non-union of long bone fracture.

In the past, many physicians remained skeptical in attitude toward orthotripsy because of lack of basic scientific documentations despite good clinical data and few sporadic animal experiments. Now, things had changed dramatically. The results of many basic researches had demonstrated that shockwave application produced biological responses at the tissue level including the induction of neovascularization associated with increased expressions of angiogenic growth factors (eNOS, VEGF, PCNA and BMP etc). The discovery had changed the concept of shockwave from pure physical and mechanical implications to biological mechanism.

Therefore, in musculoskeletal tissues, shockwaves manifested themselves as biological mechanotransduction which differs from shockwaves in urology (Orthotripsy). The preliminary results of other recent studies in animal models also showed that high-energy shockwaves might be associated with the release of NO free radicals and cell apoptosis by altering Wnt and DKK-1 molecules at the sub-cellular level. Based on this new concept, many new indications of shockwaves other than musculoskeletal disorders had been reported including but not limited to chronic skin lesions, osteonecrosis of the femoral head, stable angina pectoris, second degree burn, plastic flap reconstruction and antibacterial application etc. These new indications had widely opened up the field of shockwave in clinical application.

Currently, there are many unsettled issues that ISMST must play a role to resolve them.

1. Many shockwave devices are manufactured with different mechanical principles including electrohydraulic, electromagnetic and piezoelectric. Each device recommended its own energy levels and the numbers of treatment, and the information are not interchangeable in mathematical and physical models.

2. There has been no clear definition on “high-energy” and “low-energy” shockwaves based on scientific data.

3. There is no study documenting the dose-response effect of shockwave despite the fact that the time- and dose-dependent effects of shockwaves were observed in clinical application.

4. It was speculated that NO free radicals might be involved in the signal transduction and mediation of physical shockwave at the sub-cellular level. Obviously, further studies are needed including genome micro-array analysis to validate the actual biological mechanism of shockwaves in musculoskeletal tissues.

5. In clinical application, shockwave should be recommended as one of the initial choices of treatment for acute and chronic insertional tendinopathies rather than only for chronic refractory conditions of 6 months or longer duration.

6. Furthermore, the off-label indications of FDA guidelines such as osteonecrosis of the femoral head, knee and ankle, OCD of the knee and ankle, infrapatellar tendonitis (jumper knee), chronic skin ulcers, non-union of long bone fracture and stress fracture etc should be recommended as routine practice.

7. The last and the most important issue is that shockwave should be regarded as a surgical procedure since shockwaves cured most diseases with one single treatment. Unfortunately, many third party insurances regarded shockwave as a therapy modality and reimbursed the cost of treatment unfavorably. Therefore, the term of “Shockwave therapy” to be changed to “Shockwave biosurgery” similar to other procedures such as radiosurgery. This change may assist the insurance companies to properly reimburse the cost of shockwave treatment.

Under the leaderships and the guidelines of ISMST, we together have made significant improvement in the field of musculoskeletal shockwaves in the past many years. However, we must work harder and closer together to further strengthen the biological concept and the clinical implication of shockwaves to our peers, and make this new effective and safe, non-invasive and non-surgical device available to patients in need worldwide.

Inside this Issue

Editorial comments	1
Physics and technology of shock wave and pressure wave therapy	2
Extracorporeal Shock Wave Therapy (ESWT) in Skin Lesions.....	13
Instructions for Authors	15

Physics and technology of shock wave and pressure wave therapy



Othmar Wess

Physicist
Director Product Development / Marketing
STORZ MEDICAL AG

Zusammenfassung

Extracorporal erzeugte Stosswellen wurden erstmals 1980 zur Zertrümmerung von Nierensteinen eingesetzt und sind seitdem zur Methode der Wahl bei den meisten Steinen in Niere und Harntrakt geworden. Neben der Anwendung in der Lithotripsie werden Stosswellen seit den 90er Jahren zunehmend für eine Reihe von Indikationen im muskuloskeletalen Bereich mit Erfolg angewendet. Stosswellen sind eine Form mechanischer Energie, die ohne Verletzung der Körperoberfläche durch die Haut in den Körper eingeleitet und in vorherbestimmten Tiefen zur Wirkung gebracht werden kann. Erzeugt werden Stosswellen in der Medizin durch elektrohydraulische, piezoelektrische oder elektromagnetische Verfahren. Die mechanischen Wellen werden mit akustischen Linsen oder Reflektoren fokussiert und mit Hilfe von bildgebenden Verfahren auf Zielgebiete im Körper gerichtet. Zur Charakterisierung der Stosswellenfelder werden die Parameter Druck, Energie, Energieflussdichte und verschiedenen Definitionen für die Fokus- und Behandlungszone verwendet. Neben der mechanischen Kraftentfaltung an akustischen Grenzflächen wird auch im Gewebe Kavitation erzeugt, die sekundär zu nadelstichtartigen Belastungen von Grenzflächen führt. Auf Grund dieser Kräfteinwirkungen sind einerseits Fragmentationseffekte an spröden Materialien (Nierensteine etc.) oder auch stimulierende Effekte wie Erzeugung von Aktionspotenzialen an Nervenzellen und biologische Reaktionen durch Freisetzung verschiedener Stoffe zu verzeichnen. Obwohl speziell die biologischen Wirkungsmechanismen weitgehend unbekannt sind, wird die Stosswellentherapie erfolgreich zur

Steigerung der Blutversorgung und von Stoffwechselprozessen eingesetzt. Letztendlich werden dadurch biologische Prozesse angeregt, die zu einer dauerhaften Heilung führen.

Summary

Extracorporeally generated shock waves were first used for kidney stone fragmentation in 1980. They became the method of choice for most kidney and ureteral stones. More than 10 years later, shock waves were successfully utilized for the treatment of several musculoskeletal diseases. Shock waves are mechanical waves passing through the surface of a body without injury and may act therapeutically in predetermined areas within the body.

Shock wave generation makes use of three different principles: electrohydraulic, piezoelectric and electromagnetic. They are focused using spherical arrangements, acoustical lenses or reflectors. For targeting distant treatment areas within the body, ultrasound or X-ray localization devices are used. Important parameters are pressure, energy, energy flux density and different definitions for focal and treatment areas. Besides mechanical effects on acoustic interfaces, cavitation bubbles are generated which, in turn, cause needle-like punctures at interfaces. Due to both effects, fragmentation of brittle material such as kidney stones and stimulating effects such as the generation of action potentials of nerve cells take place. Biological reactions of liberation of different agents are reported. Shock waves are successfully applied to increase local blood circulation and metabolism, although the biological working mechanism is still not completely known. Final healing is considered due to these effects.

Introduction

For the first time in February 1980 kidney stones were successfully fragmented in the body of a patient using externally applied shock waves. The mechanical energy of the shock wave was able to be transmitted to the body and brought into effect on the stone without significant damage to the tissue. The granular fragments were flushed out of the body in a natural way, eliminating the need for an invasive operation, which had been usual up to that time. This date marks the beginning of a new era characterised by the targeted application of therapeutically effective acoustic energies in human tissue. The special feature of this new form of energy in the medical field is the possibility of generating the energy outside of the body and bringing it into effect on target areas deep inside the body without damaging the surrounding tissue. A new form of energy is thus available in addition to the known forms of ionising radiation for a multitude of medical applications.

At the end of the 1960s, the idea arose to generate shock waves in order to fragment body concretions such as kidney stones and gallstones from outside without contact. The procedure was developed by the Dornier Company in Germany in the 1970s. With the first successful lithotripsy in a human being^{1,2,3} this became the method of choice for almost all kidney stones and stones in different areas of the ureter.

After the successful fragmentation of kidney stones, the procedure was extended with varying degrees of success to stones in the gallbladder⁴, in the common bile duct⁵, in the pancreas⁶ as well as in the salivary ducts^{7,8,9}.

The idea of using shock waves to dissolve calcium deposits in the shoulder¹⁰ or in the areas at which the tendons are attached¹¹ arose. Although experts could not expect a direct fragmentation effect due to the mostly soft consistency of the calcium deposits compared to hard and brittle kidney stones, surprisingly the treatments were frequently successful. This demonstrated a new effect of shock waves on living tissue, namely the initiation of healing processes due to improved metabolism and increased local circulation. Today, shock waves are used to treat pseudoarthrosis^{12,13}, and even in cardiology to treat angina

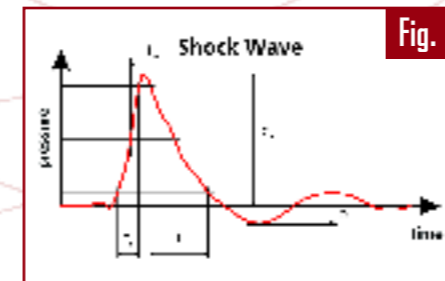
pectoris¹⁴. There are already indications for further areas of application, so that the potential of shock waves in medicine seems to be far from exhausted.

In order to prevent reflection losses during the transition into the body, the shock wave must not be generated in air but in a medium with similar acoustic properties as those of human tissue. Generating shock waves in a water bath that is brought into contact with the patient's skin directly or via a coupling diaphragm is a good solution.

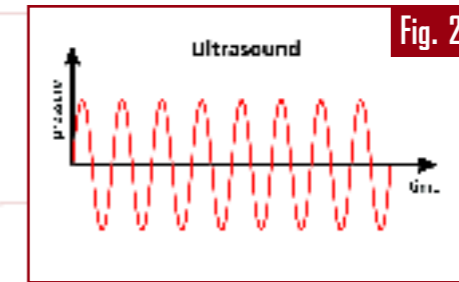
What are shock waves?

Shock waves appear in the atmosphere when explosive events occur, such as when explosive material is detonated, lightning strikes or when airplanes break the sound barrier. Shock waves are acoustic waves that are characterised by high pressure amplitudes and an abrupt increase in pressure in comparison to the ambient pressure. In the atmosphere, shock waves can be heard directly as loud "bangs". They can transmit energy from the place of generation to distant areas and may cause window panes to shatter, for example.

Despite their relationship to ultrasound, shock waves basically differ by having especially large pressure amplitudes. For this reason, steepening effects due to non-linearities in the propagation medium (water, human tissue) have to be taken into consideration. In addition, ultrasound usually consists of periodic oscillations with a limited bandwidth, whereas shock waves are represented by a single, mainly positive pressure pulse that is followed by comparatively small tensile wave components. Such a pulse contains frequencies from several kilohertz to more than 10 megahertz. (Fig. 1, 2)



Time/pressure profile of a shock wave. The rise to peak pressure (p+) takes place in a few nanoseconds (ns). The peak pressure reaches values of approx. 10-150 megapascals (MPa). The pulse lasts approx. 0.3-0.5 μs. The relatively low tensile wave component (p-), which is limited to approx. 10% of the peak pressure, is characteristic.



In comparison to shock waves, ultrasound is represented by a periodic oscillation of a limited duration.

Mechanisms for generating shock waves Electrohydraulic shock wave generation

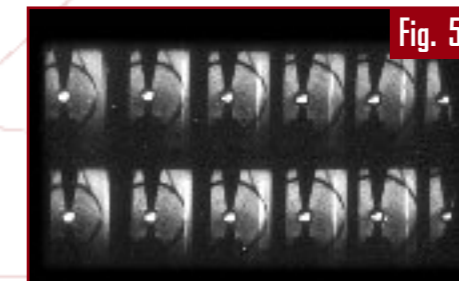
The method initially developed by Dornier is similar to a lightning strike. A high-energy electrical discharge across a spark gap is ignited in a water bath. (Fig. 3, 4, 5)



Electrode/tip configuration for generating electrohydraulic shock waves through underwater spark discharge.

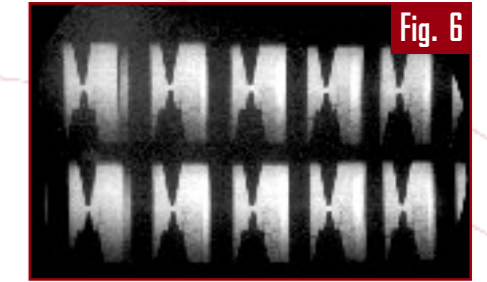


High-speed recording of a spark discharge (Frame rate: 2 x 10⁶ frames per second). The spark ignition takes place in frame 2 of the upper row. A plasma bubble subsequently forms. A shock wave cannot be detected yet. It has already detached itself between the second frame of the first row and the second frame of the second row.



High-speed recording of a spark discharge (Frame rate: 10⁶ frames per second). The frame rate magnified by a factor of 50 shows the propagation of the spherical shock wave around the spark. The shock wave has already separated itself from the plasma bubble in the centre. The plasma bubble continues to grow independently of the shock wave for approx. 1-2 milliseconds.

A capacitor charged with approx. 20 kilovolts (kV) is connected with two metal electrodes arranged at a distance of approx. 1 mm via a fast high-voltage switch. A thin current path, a so called leader, first develops, which connects the two electrodes with each other. (Fig. 6)



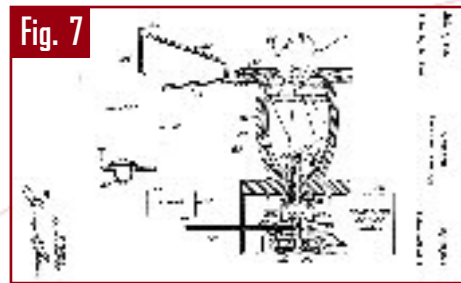
Before the actual ignition of the spark, so-called "leaders" form, which create a conductive connection between the electrodes. When one of these leaders has created a bridge to the opposite electrode, the current channel can expand explosively by discharging the stored energy. (Frame rate: 10⁶ frames per second)

The formation of the leaders requires some time, during which a path with increased conductivity spreads from one electrode to the opposite one. A bundle of different leaders is formed, similar to the growth of a plant with several shoots. As soon as one branch of the bundle reaches the electrode on the opposite side, the conductivity between the electrodes is established. An increasing avalanche of current rapidly heats up this current channel. A hot plasma forms, which explosively expands at supersonic speed over the first millimetres and strongly compresses the surrounding liquid. Pressure peaks of more than 100 megapascals (MPa) = 1000 bar are generated within a few nanoseconds.

The pressure disturbance spreads radially around the spark as a spherical, divergent wave into the surroundings and thereby rapidly loses intensity. After a few millimetres, the pressures have subsided to the point that a regular propagation takes place without taking significant non-linearities into account.

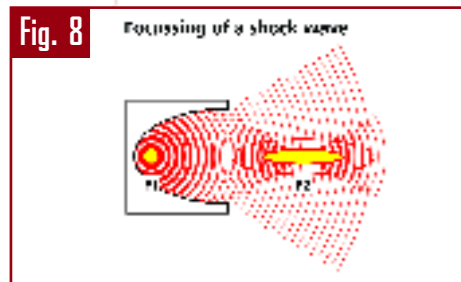
For many indications, such as e.g. the fragmentation of kidney stones, an effect deep within the body, away from the originating point, is desired. To this end, the shock waves are focused with an ellipsoid-shaped reflector, in the first focal point of which the underwater spark gap is generated. A corresponding arrangement was already proposed by

Frank Rieber in 1947 to treat biological tissue. (Fig. 7)



American patent (Rieber) from 1951. It already shows the principle of electrohydraulic shock wave generation and the planned application for biological tissue.

A considerable part of the primary spherical wave is directed outside of the reflector into the second focus of the semi-ellipsoid by the reflection on the reflector surface. The shock wave pressure can be increased to values of several ten megapascals in the vicinity of the second focus and used for therapeutic purposes such as lithotripsy. Focusing makes it possible to locally limit the treatment area and prevent side effects to a large extent. (Fig. 8)



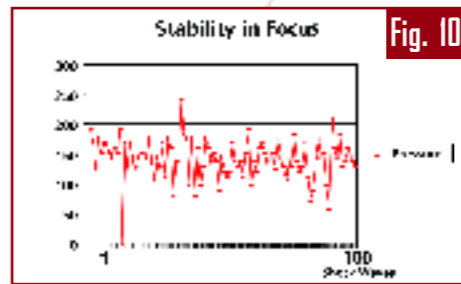
Principle of focusing shock waves using a rotation ellipsoid. The primarily divergent spherical shock wave is generated in the first focus F1 and transformed through reflection into a convergent spherical wave that is concentrated in the second focus F2. In addition to the focused wave, part of the primary wave continues to pass divergently out of the reflector.

A disadvantage of generating shock waves with underwater spark gaps is that the sparkover and thus the location of the shock wave creation varies spatially due to stochastic fluctuations. After a few thousand shock wave pulses, the electrodes have to be replaced with new ones. The electrode spacing is increased beyond a critical limit by the wear of the electrodes, which prevents a spark over. Even before this occurs, the location of the spark over can no longer be precisely controlled. An example of an irregular spark over (misfire) is shown in Fig. 9. As a consequence, considerable pressure fluctuations can be observed in the focus zone from shock to shock (Fig. 10). For this reason, pressure values given for electrohydraulic

generators are always averaged over several shock waves, from which the current individual values can considerably deviate.



High-speed recording of an irregular spark discharge (frame rate: 2×10^6 frames per second). The propagation of a bent, hose-shaped plasma bubble can be recognized. This is caused by a spark that does not take the direct path between the electrode peaks but attaches to the side of the electrodes. Precise focusing through a rotation ellipsoid is no longer guaranteed because of the deviation from the spherical geometry.

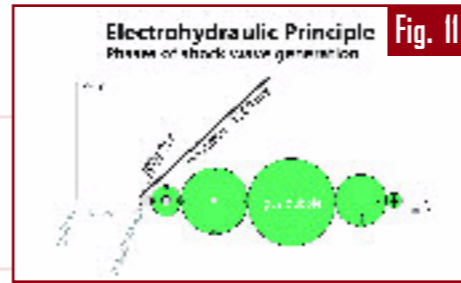


Pressure measurement in the second focus of an electrohydraulic shock wave generator. Due to the stochastic variations in the location at which the spark ignition takes place near the first focus, the shock wave pressure varies in the second focus from shock wave to shock wave.

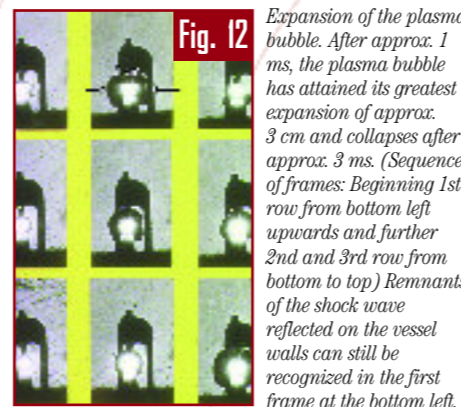
To make matters worse, electrohydraulically generated shock waves cannot be controlled so well and are sometimes perceived as very painful and loud, especially at the low pressure settings that are frequently required for orthopaedic applications. The reason for this is that the plasma bubble expands up to several centimetres. After the shock wave has detached itself from the plasma bubble, the bubble grows to a volume of several cubic centimetres within 1-2 milliseconds. The expansion of the bubble comes to a stop and is followed by a rapid collapse after approx. 3 milliseconds. The whole process is perceived as an explosive sound but does not contribute to the actual shock wave, since this has already moved approx. 1 metre away. The chronological process of the electrohydraulic shock wave generation is shown in Fig. 11, 12.

After the overwhelming success of shock wave lithotripsy for kidney stones, it therefore stood to reason to look for alternative methods of shock wave generation that did not have the

above mentioned disadvantages of the electrohydraulic method.



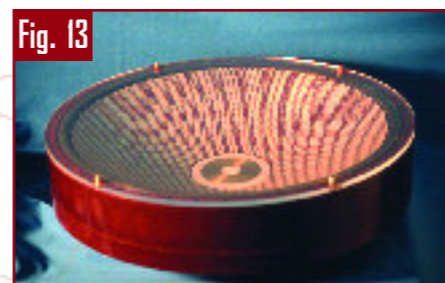
The phases of the electrohydraulic shock wave generation are represented on the time axis. After the high voltage is applied to the electrode peaks, a "leader" that determines the path of the spark initially develops with a delay. As soon as a conductive bridge exists between the peaks, the stored electrical energy flows through the spark and explosively heats up the path. The bubble only expands at supersonic speed (approx. 2000 m/s) immediately after the ignition. As soon as the propagation of the plasma bubble falls below supersonic speed (approx. 1500 m/s), the shock wave separates from the bubble. The bubble continues to expand with reduced speed independently of the shock wave and collapses after approx. 3 milliseconds (ms), long after the shock wave has separated.



Expansion of the plasma bubble. After approx. 1 ms, the plasma bubble has attained its greatest expansion of approx. 3 cm and collapses after approx. 3 ms. (Sequence of frames: Beginning 1st row from bottom left upwards and further 2nd and 3rd row from bottom to top) Remnants of the shock wave reflected on the vessel walls can still be recognized in the first frame at the bottom left.

Piezoelectric shock wave generation

Electroacoustical transducers are known from ultrasound technology experience a pulse-like displacement using the piezo effect when a voltage pulse of several kilovolts (kV) is applied. If a large number of piezoelectric elements are arranged on a spherical shape, they can be displaced in the direction of the centre of the spherical shape by synchronous excitation. A convergent spherical wave thus spreads out, which increases its pressure amplitude to therapeutically effective values on its way to the centre. In contrast to the electrohydraulic method, one cannot speak of shock waves in the previously defined sense until the area of the focal zone, i.e. in the centre of the spherical shape. Due to non-linearities a steepening takes place forming a shock wave in the physical sense. (Fig. 13)



Piezoelectric shock wave generation. Piezoelectric elements are arranged on a spherical surface and are synchronously excited by an electrical pulse to emit a pressure wave in the direction of the centre of the spherical surface. The process is self-focusing.

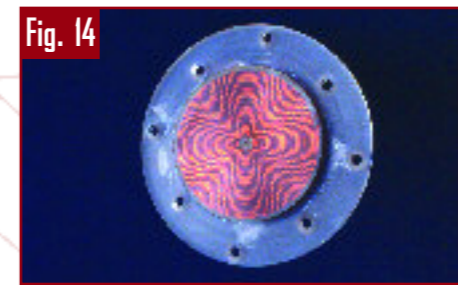
Piezoelectric systems have a high accuracy of repetition and are easy to control even in low energy ranges. Pressures of up to 150 MPa (1500 bar) are attained in very small focal spots. Unlike electrohydraulic technology, it is not necessary to frequently change electrodes. Despite the large-area spherical shape, the attainable total energy of the radiated shock wave can be regarded as rather low. In modern systems, this disadvantage is partially compensated by using double layers of piezoelectric electroacoustical transducers.

Electromagnetic shock wave generation

The method of electromagnetic shock wave generation is based on the physical principle of electromagnetic induction, as used for example in loudspeakers. The arrangement of coils and membranes is optimized to generate powerful and short acoustical pulses. Two different configurations can be distinguished: 1. the flat coil with focusing through an acoustical lens and 2. the cylindrical coil with a parabolic reflector.

In the case of the **flat coil with focusing** by an acoustical lens, a spirally wound coil that is separated from an electrically conductive metal membrane by a thin insulation layer is placed on a flat surface. If a short current pulse flows through the coil, a magnetic field is formed around the individual windings of the coil. This field penetrates through the insulation layer into the metal membrane. Due to the fast current increase, eddy currents are induced in the membrane, which in turn create a magnetic field that is opposed to the original magnetic field. This yields repellent forces that

abruptly press the membrane from the coil into the adjacent water bath. The pressure disturbance created in this way spreads out as a plane pulse wave into the transmission medium until it is transformed into a convergent spherical wave by an acoustical lens. (Fig. 14, 15)



Electromagnetic shock wave generation, flat coil. A flatly wound coil is covered with an insulation layer and a conductive membrane. An electric shock generates repellent electromagnetic forces that radiate a cylindrical pressure wave at an angle to the cylinder axis, according to the geometry of the arrangement. The wave is transformed into a convergent spherical wave through reflection on the paraboloid reflector and is concentrated in the treatment zone.



The plane wave is transformed into a convergent spherical wave using acoustical lenses and concentrated in the treatment zone.

This method eliminates the need to replace electrodes as expendables and is also easy to control, just as with the piezoelectric method. The energy output can be considered good. A certain disadvantage can be seen in the fact that the possibilities for focusing with acoustical lenses come up against the technical limits of the lens material. Therefore, only shock wave sources with restricted diameters and limited aperture angles can be generated, so that the shock wave energy is induced in the body through relatively small areas of skin. Pain in the coupling area thus cannot be entirely prevented.

In the case of a **cylindrical arrangement** of the coil, on the other hand, a divergent cylindrical wave is primarily generated, which is transformed into a convergent spherical wave using a special rotation paraboloid. Regardless of the technical limitations of the lens material, it is possible to design reflectors with large diameters and a

great depth of focus that concentrate the primarily generated pressure waves on the treatment zone in a highly efficient way (Fig. 16). The shock wave field of an electromagnetic cylinder source is shown in Fig. 17.



Electromagnetic shock wave generation, cylinder coil and paraboloid reflector. A coil is wound around a hollow cylinder and covered with an insulating layer and a conductive membrane. An electric shock generates repellent electromagnetic forces that radiate a cylindrical pressure wave at an angle to the cylinder axis, according to the geometry of the arrangement. The wave is transformed into a convergent spherical wave through reflection on the paraboloid reflector and is concentrated in the treatment zone.



Schlieren photograph of the fronts of successive waves on the way from the reflector to the treatment zone.

Due to the large apertures and the according large aperture angle, the shock wave energy can be distributed over a large surface area of the body with little pain and can be narrowly concentrated on the focal zone inside the body at the same time. In addition, this makes it easily technically possible to integrate location devices such as ultrasound transducers or X-ray paths "in-line" on the axis of the shock wave head, in order to treat target areas deep in the tissue with high precision.

In the case of both electromagnetic shock wave generators as well as piezoelectric methods, shock waves in a physical sense are not generated until the focal zone, when the pressure amplitudes have become so high that steepening effects are activated by non-linear propagation. The steepening of a wave into a shock wave is shown in Fig. 18.

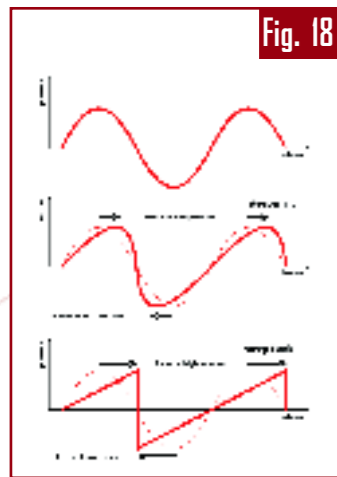


Fig. 18 Schematic representation of the steepening of a wave front due to non-linearities in the propagation medium. The wave runs faster in zones with higher pressure and thereby steepens to form a shock wave front.

All of the described generation methods are used in different equipment designs from various manufacturers. In the past few years, however, a trend towards electromagnetic generation methods has become apparent, since these not only eliminate the annoying job of replacing electrodes but also allow the applied shock wave energy to be dosed very precisely and sensitively.

Propagation of shock waves (reflection, refraction and scatter)

As acoustical waves, shock waves require a medium for propagation. In the case of medically used shock waves, it is usually water in which the shock waves are generated and biological tissue in which they are brought into effect. The pressure is transmitted through the displacement of mass particles, as shown in Fig. 19.

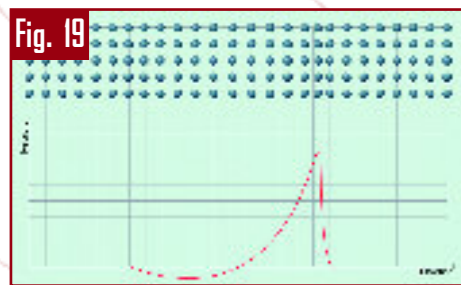


Fig. 19 Propagation of a shock wave (schematic) through displacement of particles from the rest position and their springing back to rest position. The diminished pressure component of the wave is caused by particles that overshoot.

The water bath is important for the medical application of shock waves because the transition to body tissue takes place without a significant

change in the acoustical impedance. Acoustical interfaces at which the acoustical properties of density (ρ) and sound velocity (c) change produce a deviation from the straight propagation of waves due to familiar optical phenomena such as refraction, reflection, scatter and diffraction. These effects must be taken into consideration when applying shock waves to human beings, in order to ensure that the energy can become effective in the treatment zone. On the other hand, these properties of shock waves can be used to selectively focus and locally release energy in particular areas of the body. (Fig. 20, 21)

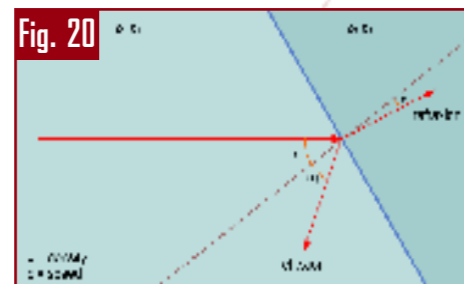


Fig. 20 Reflection and refraction of shock waves at interfaces with a different acoustic impedance (density $\rho \times$ sound velocity c).

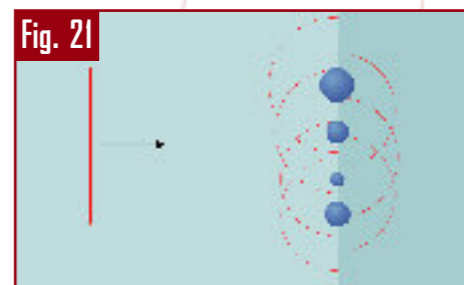


Fig. 21 Shock waves are scattered by obstacles such as rib bones and gas bubbles.

As previously mentioned, the generation of shock waves in a water bath or a tissue-like medium is decisive for preventing a large part of the energy from being lost through reflection when it is induced into the body. For this reason, the first device for kidney stone fragmentation required the patient to be submerged in a water-filled tub. Today's devices work with the so-called "dry" coupling, with which the water bath is connected to the body via a flexible diaphragm. Regardless of this, it must be ensured that no organs that contain gas (lungs) or large bone structures are in front of the actual treatment area that shield the target area from the shock waves and thus prevent the desired therapeutic effect.

It must also be assumed that soft tissues (skin, fat, muscles, tendons

etc.) are not acoustically homogenous or without interfaces either. However, the differences in the acoustical properties are considerably less than for the transition from water to air and vice versa. In addition to absorption and reflection, refraction effects occur here that can lead to deviations from the straight propagation of shock waves in the body that are difficult to control.

Shock wave parameters/ measurement of shock waves Shock wave pressure

Shock waves are mainly characterised using measurements with pressure sensors¹⁵. This requires a very small sensor with a high load capacity and wide frequency response. As shown in Fig. 22, the measurement of a shock wave field consists of a multitude of point measurements at different places in the shock wave field.

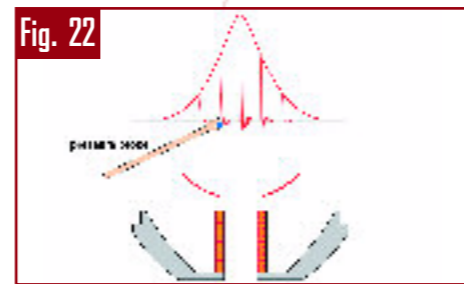


Fig. 22 Shock wave fields are measured with a pressure sensor by recording the chronological pressure curves at different places in the field. All other parameters are calculated from the pressure values plotted over time.

In each measurement, the peak pressure p_+ as well as the time profile of it with rise time t_r , pulse duration t_w , tensile phase p_- etc. are measured. Shock waves used in medicine show typical pressure values of approx. 10-100 megapascals (MPa) for the peak pressure p_+ . This corresponds to 100-1000 times the atmospheric pressure. The rise times t_r are very short at around <10-100 nanoseconds (ns), depending on the type of generation. The pulse duration t_w of approx. 0.3-0.5 microseconds (μ s) is also quite short (in comparison to the medical pressure waves described further below). Another characteristic of shock waves is the relatively low tensile wave component p_- , which is around 10% of the peak pressure p_+ .

The further parameters of the shock wave field are calculated from this data in a rather complicated

procedure. If the peak pressures p_+ that were measured at various locations in the shock wave field are plotted in a three-dimensional representation (in the axial direction of the shock wave propagation and vertically to this as well), a pressure distribution like the one shown in Fig. 23 results.

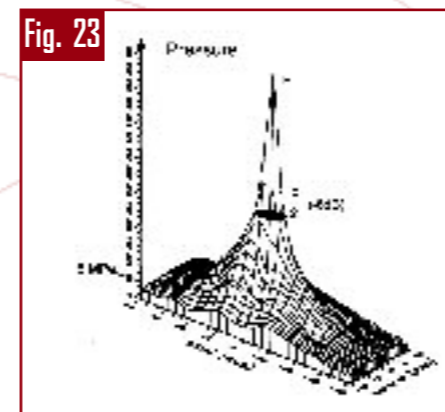


Fig. 23 Pressure distribution in a plane of the shock wave field, axially in the direction of the propagation of the shock wave and in a lateral direction to this. The peak value p_+ measured at the respective location in the shock wave field is plotted.

Obviously shock wave fields do not have sharp boundaries, but the shape of a mountain with a peak in the centre and more or less steeply falling slopes. One therefore speaks of a pressure distribution. Different shock wave devices differ in the shape and height of this pressure distribution, for example.

-6 dB shock wave focus

For the selective treatment of locally limited areas in deeper tissue layers (pseudoarthrosis, femoral head necroses, kidney stones ...), shock waves are bundled to be able to correspondingly limit the desired effects. The highest pressure values are measured in the compression zone. If the pressure sensor is moved away from the centre of compression, the pressure values continually decrease. As a result of the physical characteristics, it is not possible to draw a sharp boundary beyond which pressures abruptly fall to zero. For this reason, it is not possible to sharply define the effective zone of the shock wave with a fixed spatial contour either. Physically, the focal zone is defined as the area of a shock wave field in which the measured pressures are greater or equal to half of the peak pressure measured at the centre (Fig. 24).

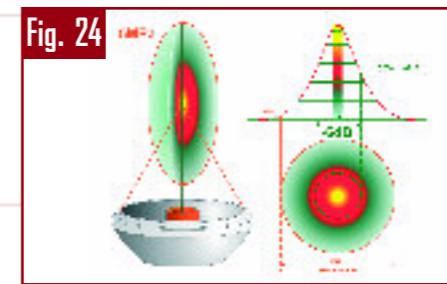


Fig. 24 Representation of the -6 dB focus (defined by the area above half of the peak pressure, $1/2 p_+$) and the 5 MPa treatment zone (defined by peak pressures $p > 5$ MPa).

The area defined in this way is also called the -6 dB focus or described with the abbreviation FWHM (Full Width at Half Maximum). This is thus a spatial area in relation to the peak pressure, which, however, does not initially provide any information on the energy contained therein or the biological effect.

5 MPa treatment zone

Only together with energy information is it possible to give an impression of the area in which the shock wave will unfold its biological effect. In other words: The treatment area of a shock wave in the body is not described by the size of the (-6 dB) focus. It can be larger or smaller. A further value was therefore defined that is more closely related to the treatment zone and is not related to relative quantities (relationship to the peak pressure at the centre) but to an absolute quantity, namely the pressure of 5 MPa (50 bar). The 5 MPa focus¹⁵ was correspondingly defined as the spatial zone in which the shock wave pressure is greater than or equal to 5 MPa. If a certain pressure limit is assumed to exist, below which a shock wave has no or only minor therapeutic effect, this is taken as a measure and assumed to be 5 MPa here with certain arbitrariness. Even if this value had to be corrected in the future according to the indication, this definition has the advantage that it reflects the change in the treatment zone with the selected energy setting.

The different zones and their changes according to the selected energy levels are schematically represented in Fig. 25.

In this example, it can be seen that the -6 dB focal zone does not become larger or smaller despite different energy settings. When the energy increases, however, it can be

assumed that the effective zone of the shock waves will increase in size. This is expressed in the increasing size of the 5 MPa zone.

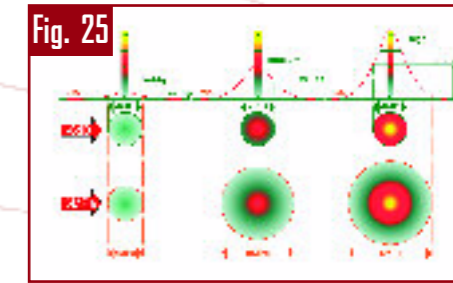


Fig. 25 -6 dB focus in comparison to the 5 MPa treatment zone with different energy settings: low, medium and high. Despite the different energy contents, the dimensions of the (-6 dB) focus remain almost unchanged. The 5 MPa treatment focus increases along with the energy level and thereby demonstrates the expanded activity area of the shock waves.

Energy (E)

The energy of the applied shock wave is an important parameter for practical applications¹⁵. It can be assumed that the shock wave only has an effect on the tissue when certain energy thresholds are exceeded. In addition to the time curve of the shock wave $p(t)$ (see Fig. 1), the surface A , in which the pressure can be measured, is also decisive. Using the acoustical parameters of the propagation medium density (ρ) and sound velocity (c) yields the following equation for energy:

$$E = A/\rho c \int p(t)dt$$

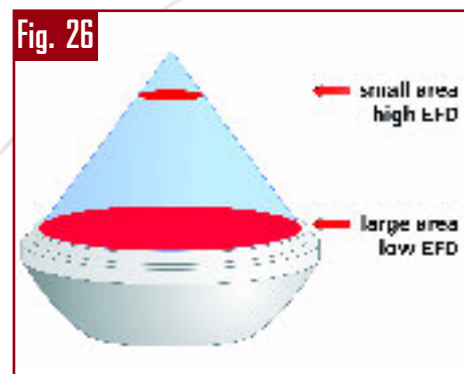
A distinction is made as to whether integrating the pressure over time only records the positive pressure components (E_+) or the negative (tensile) components (E_{total}) as well. The total energy is usually given with E (without index). The acoustical energy of a shock wave pulse is given in millijoules (mJ). As a rule, several hundreds or thousands of shock wave pulses are emitted per treatment, so that the total emitted energy is yielded by multiplication by the number of pulses.

Energy flux density (ED)

As previously mentioned the therapeutic effect of shock waves is affected by whether the shock wave energy is distributed over a large area or concentrated on a narrow treatment zone. A measure of the energy concentration is obtained by calculating the energy per area (E/A): $E/A = 1/\rho c \int p(t)dt = ED$ (energy flux density)

The energy flux density ED is given in millijoules per square millimetre (mJ/mm^2). In the case of energy flux density, one also distinguishes between integration over the positive part of the pressure curve or the negative part as well¹⁵. Without index (EFD), the pressure curve is usually considered including the negative (tensile) components.

The effect of the focusing on the energy flux density is schematically represented in **Fig. 26**.



With the same total energy, the energy flux density increases with focusing. Reducing the area concentrates the energy and thus increases the effect of the shock wave.

The above parameters are usually sufficient to characterise a shock wave field well for medical applications. Shock wave devices that work with different generation principles can differ in relation to the listed parameters. The “quality” of the shock waves used in the treatment zone should be independent of the generation principle, however. In other words: The measurement of the above parameters in the treatment zone does not allow any fundamental conclusions to be drawn about the type of generation. “Electrohydraulically generated shock waves are not better or worse than piezoelectrically generated shock waves”, although secondary parameters such as repeat accuracy, meterability, energy range, operating costs for expendables etc. can naturally differ.

Note that the above parameters are usually measured in water. Due to the inhomogeneities in tissue, however, deviations from the straight propagation of shock waves lead to a spatial expansion of the focal zones. With increasing depth in the body, the peak pressure as well as the energy flux density will therefore decrease compared to a measurement in a water bath.

Physical effects of shock waves

Direct effect on interfaces

Shock waves have different characteristics as compared to ultrasound. Ultrasound has a high-frequency alternating load on the tissue in the frequency range of several megahertz that leads to heating, tissue tears and cavitation at high amplitudes. One factor, on which the effect of shock waves is based, is on a forwards-directed dynamic effect (in the direction of the shock wave propagation). A momentum acts at the interface that can be increased up to the destruction of kidney stones. (**Fig. 27**)



Effect of a focused shock wave on a cube-shaped artificial stone with an edge length of 10 mm. (Shock wave occurrence from the right). One can see the stone held on a wire, the fragmentation into a few pieces and cavitation bubbles in the shock wave path.

Since these dynamic effects basically occur at interfaces with a jump in the acoustical resistance but hardly ever in homogenous media (tissue, water), shock waves are the ideal means for creating effects in deep tissue without interfering with the tissue in front of it. However, even less distinct interfaces within soft tissue structures experience a small dynamic effect from shock waves. Topics of discussion include the mechanical destruction of cells, membranes and bone trabeculae¹⁶, for example, as well as the stimulation of cells through reversible deformation of the cell membrane.¹⁷ As long as the treated areas are not on the skin surface, the focusing also makes it possible to increase the effectiveness in the treatment area while simultaneously reducing side effects outside of this area.

This yields very different effects on the tissue, which on the one hand lead to a primary destruction or irritation or to healing processes through

stimulation, which can be observed with orthopaedic applications in particular. As a consequence of shock wave therapy, an increased local circulation and a more intense metabolism can usually be observed, to which the resulting healing can be attributed.

Indirect effect Cavitation

In addition to the direct dynamic effect of shock waves on interfaces, so-called cavitation occurs in certain media such as water and sometimes in tissue as well.¹⁸ Cavitation bubbles occur directly after the pressure/tension alternating load of the shock wave has passed the medium. A large number of bubbles grow until approx. 100 microseconds after the wave has passed and then violently collapse while emitting secondary spherical shock waves (**Fig. 28**).

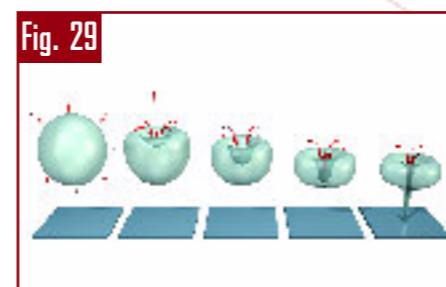


Cavitation bubbles created by a shock wave running from bottom to top. Directly behind the shock wave, the bubbles are still small. They grow within approx. 30 microseconds and then collapse while emitting a secondary (spherical) shock wave (circular rings at the bottom of the frame).

Near interfaces, cavitation bubbles can no longer collapse without being disturbed. The medium flowing back into the bubble (water, bodily fluid) can no longer flow unhindered, and the bubble therefore collapses asymmetrically while developing a microjet.¹⁹ As shown in **Fig. 29**, this fluid jet is directed at the interface with speeds of several hundred metres per second.

The jets have great energy and penetration power, so that they not only erode the hard interfaces of stones but can also penetrate the walls of small vessels. This causes micro bleeding or membrane perforations. The cavitation is not exclusively limited to the focal zone, but is especially pronounced there. Cavitation is another biologically effective mechanism that is available

with shock waves, which can be selectively used in localized areas, even in deeper tissue layers. The physically induced energy can elicit biological reactions via different action mechanisms. Frequently, these actions initially lead to an improved local circulation and then activate repair mechanisms as a result. In addition to the direct mechanical effects in tissue, stimulation effects can also be detected in the nervous system, which may correct pathological reflex patterns and in the process lead to a lasting recovery.²⁰



Cavitation bubbles near obstacles cannot collapse in a spherically symmetrical way, since the obstacle hampers the flow of the fluid. This causes the development of microjets that hit the interface at several hundred metres per second and leads to erosion or punch needle-like holes in vessels or membranes there (schematic).

Selective application of localized shock waves

Technical equipment for shock wave application is supplied with different focal distances, depending on the penetration depth. For applications at a depth of several centimetres, the equipment must be equipped with a localization device. An X-ray or ultrasound localization is used, depending on the indication. The treatment area is represented with one of the imaging methods and brought into line with the treatment zone of the shock wave device via corresponding adjustment. Devices are offered with very different localization concepts in respect to effort, convenience, precision and localization modality.

If the zones to be treated are less than 1-2 cm below the body surface, work can generally be done without an integrated localization device. The target area can be identified using separate ultrasound or X-ray devices and indicated by simple markings on the skin. The shock wave device is placed on these marking points and the treatment carried out. Such

devices can be offered at a correspondingly low price, since a localization device is a considerable part of the total expense.

For a carefully targeted shock wave application, all deeper areas require an integrated localization device that has a precise spatial relationship to the actual shock wave applicator. If the configuration of the shock wave source allows the localization device to be centrally integrated on the shock wave axis (in-line), one has the advantage of very high localization accuracy and easy-to-interpret spatial relationships. Systems located outside of the treatment head (off-line) may be operated with some flexibility independent from it. The localization geometry, however, is more complex and generally not suited to directly detect obstacles in the shock wave path. **Fig. 30** shows a shock wave device with in-line ultrasound localization and a treatment depth of up to 15 cm. (**Fig. 30**)



Shock wave device with freely movable treatment head (electromagnetic cylinder source) and inline ultrasound localisation for surface application and target areas up to 15 cm deep.

Generation of pressure waves

In addition to the above-described shock waves, also pressure waves with different features are used in medicine. Whereas shock waves typically travel with the propagation speed of the medium (approx. 1500 m/s for soft tissue), pressure waves are usually generated by the collision of solid bodies with an impact speed of a few metres per second, far below the sound velocity. First, a projectile is accelerated, e.g. with compressed air (similarly to an air gun), to a speed of several metres per second and then abruptly slowed down by hitting an impact body. The elastically suspended impact body is

brought into immediate contact with the surface of the patient above the area to be treated, using ultrasound coupling gel if necessary. When the projectile collides with the impact body, part of its kinetic energy is transferred to the impact body, which also makes a translational movement over a short distance (typically < 1 mm) at a speed of around one metre per second (typically < 1 m/s) until the coupled tissue or the applicator decelerates the movement of the impact body.

The motion of the impact body is transferred to the tissue at the point of contact, from where it propagates divergently as a pressure wave. (**Fig. 31a, 31b, 31c**)

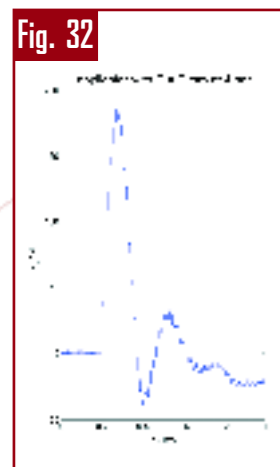


Phases of pressure waves generated by the impact of solid bodies on an impact body. The impact body transmits a pressure pulse into the coupled tissue.

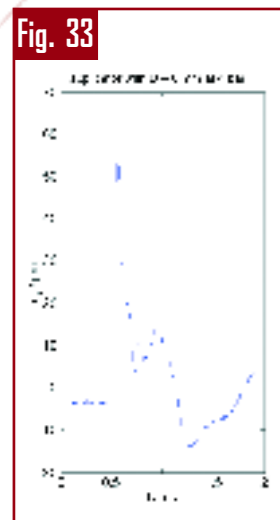
The time duration of the pressure pulse is determined by the translational movement of the impact body and lasts typically approx. 0.2-2 milliseconds in tissue. (**Fig. 32**)

To simulate the conditions when the pressure disturbance is induced into the body, the displacement of the impact plate can be investigated when in contact with water. The time profile of the displacement is damped by the coupled water (displacement approx. 0.06 mm) and slightly

distorted. (Note the changed time scale). (Fig. 33)



Displacement of an impact body after collision with a striking body in the air. The impact body is displaced approx. 0.2 millimetres (mm) within a period of approx. 0.2 milliseconds (ms).



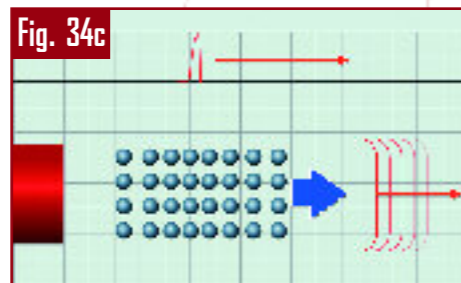
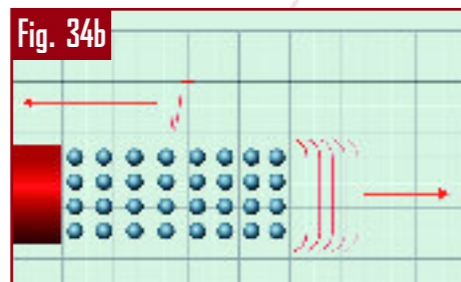
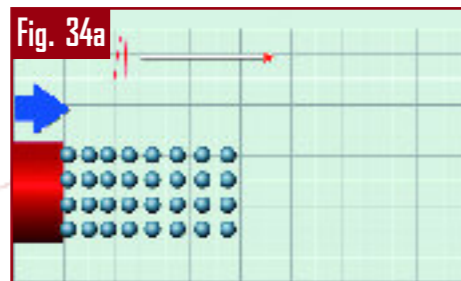
Displacement of an impact body after collision with a striking body in water. The impact body is displaced approx. 0.06 mm within a period of approx. 0.5 milliseconds. (The time scale is changed in relation to figure 11.)

As a result of its displacement, the impact body transfers a pressure disturbance to the coupled tissue, which shows the same time behaviour at the contact point as the displacement. The pressure pulses transferred to the tissue thus have duration of 0.5 ms and are longer than with the above-described shock waves by a factor of approx. 1000. At approx. 0-10 MPa, typical peak pressures with this method are lower by a factor of >10.

The extremely long pulse duration in comparison to shock waves has a decisive influence on the propagation of pressure waves in tissue. Unlike shock waves, such pressure waves cannot be focused on narrow tissue areas. In relation to the size of the human body, focusing cannot be achieved for physical reasons.

A detailed observation of the collision process between the projectile and the impact plate, however, shows a further phenomenon that can be seen in the jagged shape of the curve in Fig. 32 and to a lesser extent in Fig. 33.

The projectile and the impact body placed against the body are normally made from metal materials. When the two metal bodies collide, high-frequency harmonic oscillations (rod waves) are excited in the metal bodies. These oscillations are superimposed on the "slow" translational movement of the impact body. (Fig. 34a, 34b, 34c)

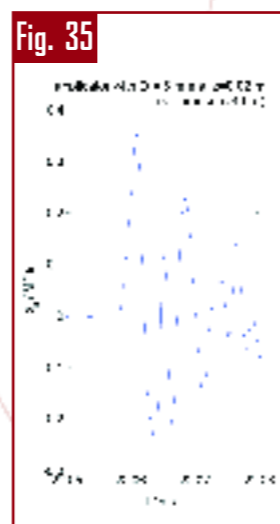


The displacement of the impact body is superimposed by a harmonic oscillation (rod waves) in the impact body. a: The projectile hits the impact body. The pressure disturbance caused by the impact passes to the distal end of the impact body and is reflected there as a tensile wave. b: After the pressure disturbance has passed through twice, the tensile wave returns to the collision point with the projectile at the proximal end of the impact body. c: Only then does the impact body detach from the projectile and move towards the coupled tissue at a speed of several metres per second. Part of the energy is already radiated into the surrounding medium at the distal end (schematic representation).

The impact of the projectile creates a pressure wave in the impact body that runs through the impact body at the typical propagation speed for the metal ($v \approx 5000$ m/s). At the distal end of the impact body, the wave is reflected as a tensile wave and returns to the collision point with the projectile. The impact body does not separate from the projectile until this wave has passed through the impact body once in both directions. As described above, the impact body begins its translational movement at a speed of several metres per second. At

the same time, the rod wave that is reflected as a pressure wave passes through the impact body once more and is reflected at the distal end again as in the first passage. The process is repeated several times, so that the described wave in the impact body is superimposed on the "slow" translational movement.

Due to the great differences in the acoustical impedance between the metal impact body and the coupled water or tissue, a large part of the energy of these high-frequency oscillations remains bound in the impact body. Only a small part of the oscillation energy is also radiated into the water and can be picked up there using the usual hydrophones. This is a damped oscillation, as shown in Fig. 35. The pressure amplitudes show values of up to 10 MPa (typically < 1 MPa) and are thus below the pressure values usually achieved by shock waves by a factor of approx. 10 to 100. A steepening due to non-linearities in biological tissue can thus be disregarded.



Measurement of the radiated harmonic oscillation displayed schematically as in figure 34. Note the changed pressure scale. The damped oscillation shows a peak pressure of less than 0.4 MPa (4 bar), which is considerably lower than that of a focused shock wave.

However, the energy contained in the high-frequency harmonic oscillation is several orders of magnitude smaller than the energy content of the aforementioned (low-frequency) pressure pulse. It is within the range of diagnostic ultrasound. Nevertheless, it cannot be ruled out that a certain treatment effect is related to this.

The previously described pressure pulse, which is long in comparison to shock waves, is difficult or impossible to detect with the common pressure sensors used in shock wave technology.

Pressure waves as described here

emanate from the application point of the impact body and travel radially into the adjacent tissue. The energy density of the induced pressure wave quickly drops with increasing distance from the application point

(by the proportion $1/r^2$), so that the strongest effect is at the application point of the application piece. One difference between focused shock waves and unfocused pressure waves is the fact that focused shock waves

can be directed into deeper tissue, where they develop a therapeutic effect, with less stress to the skin. Unfocused pressure waves, on the other hand, primarily have an effect on the surface.

Technical differences

The technical differences are shown below:

	Shock waves (focused)	Pressure waves (unfocused)	Difference
Focus	yes	no	
Propagation	non-linear	linear	
Steepening	yes	no	
Rise time	typically 0.01 μ s	typically 50 μ s	approx. 1:1000
Compression pulse duration	approx. 0.3 μ s	approx. 200 - 2000 μ s	approx. 1:1000
Positive peak pressure	0 - 100 MPa	0 - 10 MPa	10:1 - 100:1
Energy flux density	0 - 3 MJ/mm ²	0 - 0.3 MJ/mm ²	approx. 10:1

Shock and pressure waves not only differ in their physical characteristics and the technique used for generating them, but also in the order of magnitude of the parameters normally used. The differences between the most important parameters listed here are approx. 1-3 orders of magnitude.

Interestingly, the simulation effects and therapeutic mechanisms seem to be similar, despite the physical differences and the resulting different application areas (on the surface and in depth respectively). However, the described pressure waves are not able to fragment hard concrements such as e.g. kidney stones deeper in the body (> 1 cm). Nevertheless, unfocused pressure waves seem to be well suited for orthopaedic indications near the surface as well as e.g. trigger point therapy.²¹

Figure 36 shows a combination device for focused shock waves and unfocused pressure waves. Depending on the indication, treatment zones several centimetres deep in the body can be treated in a focused way and zones near the surface can be treated using unfocused pressure waves.



Combination device DUOLITH SD1 for generating and applying focused shock waves and unfocused pressure waves.

Discussion

Shock waves have become an indispensable part of medicine. They are a means of bringing therapeutically effective energies to locally limited places in the body in a non-invasive way. The fact that shock waves selectively effect acoustical interfaces and pass through homogenous elastic tissue without damage for the most part is medically important. Tissue damage outside of the treatment zone is almost completely avoided due to the possibility of concentrating energy through focusing. This significantly increases the therapeutic effects within the treatment zone, although moderate side effects (haematomas) cannot be entirely ruled out when especially high energies are used, as in lithotripsy.

In addition to the fragmentation effect in stone treatment, the stimulating effect of shock waves on biological processes has increasingly become the centre of interest in the last few years. Although the mechanism of action for this is still unknown to a large extent, shock waves seem to have a special therapeutic potential here. It appears that the principle of action is so universal that a multitude of very different indications respond positively to shock wave therapy. In order to study the mechanisms of action, the shock waves that are used must be precisely characterised using the parameters described in the text. This is the only way to determine dosage/effect relationships and obtain sound knowledge about the mechanism of action. However, the fact that the focused shock waves and unfocused pressure waves, which have clear physical differences, show a similar effect especially in the area of stimulating healing processes suggests that both forms of energy do not have a direct mechanical effect but intervene in the senso-motoric reflex behaviour. It seems that a reorganisation of pathological reflex patterns that are anchored in memory due to the stimulating effect of shock and pressure waves cannot be ruled out.¹⁹ This would open up a previously unknown potential for further therapeutic areas of application.

References

- Wess, O., Physikalische Grundlagen der extrakorporalen Stosswellentherapie, Journal für Mineralstoffwechsel, 4: 7, 2004.
- Chaussy, C., Schmiedt, E., Brendel, W.: Extracorporeally induced destruction of kidney stones by shock waves. Lancet 2: 1265, 1980.
- Chaussy, C., Schmiedt, E., Jocham, D., Brendel, W., Forssmann, B., Walther, V.: First clinical experiences with extracorporeally induced destruction of kidney stones by shock waves. J. Urol. 127:417, 1982.
- Sauerbruch, T., Delius, M., Paumgartner, G., Holl, J., Wess, O., Weber, W., Hepp, W., Brendel, W.: Fragmentation of Gallstones by extracorporeal shock waves. N. Engl. J. Med. 314:818, 1986.
- Sauerbruch, T., Stern, M. and the study group for shockwave lithotripsy of common bile duct stones: Fragmentation of common bile duct stones by extracorporeal shock waves. A new approach to biliary calculi after failure of routine endoscopic measures. Gastroenterology 96:146, 1989.
- Sauerbruch, T., Holl, J., Sackmann, M., Werner, R., Wotzka, R., Paumgartner, G.: Disintegration of a pancreatic duct stone with extracorporeal shock waves in a patient with chronic pancreatitis. Endoscopy 19:207, 1987.
- Iro, H., Nitsche, N., Schneider, T., Ell, C.: Extracorporeal shockwave lithotripsy of salivary gland stones. Lancet II, 115, 1989.
- Iro, H., Schneider, Th., Nitsche, N., Ell, Ch.: Extrakorporale piezoelektrische Lithotripsie von Speichelsteinen - Erste klinische Erfahrungen HNO 38:251, 1990.
- Kater, W., Rahn, R., Meyer, W.W., Liermann, D., Wehrmann, T.: Extracorporeal shock wave lithotripsy: New outpatient treatment concept for salivary gland stones. Deutsche Zeitschrift für Mund-, Kiefer-, und Gesichtschirurgie 14:216, 1990.
- Loew, M., Jurgowski, W., Thomsen, M.: Die Wirkung extrakorporaler Stosswellen auf die Tendinosis calcarea der Schulter. Urologe (A), 34:49, 1995.
- Dahmen, G.P., Haupt, G., Haist, J., Loew, M., Rompe, J.D., Schleberger R.: Die Extrakorporale Stosswellentherapie in der Orthopädie-Empfehlungen zu Indikationen und Techniken. In: Chaussy, Ch., Eisenberger, F., Jocham, D., Wilbert, D. (eds.). Die Stosswelle - Forschung und Klinik. Tübingen: Attempto Verlag, 1995.
- Valchanov, V. Michailov, P. High energy shock waves in the treatment of delayed and non-union of fractures. Int Orthop 15:181, 1991.
- Schaden, W., Kuderna, H.: Extracorporeal Shock Wave Therapy (ESWT) in 37 Patients with Non-Union or Delayed Osseous Union in Diaphyseal Fractures. In: Chaussy, C., Eisenberger, F., Jocham, D., Wilbert, D. (eds.) High Energy Shock Waves in Medicine. Georg Thieme Verlag, Stuttgart 1997.
- Gutersohn, A., Caspari, G., Marlinghaus, E. Autoangiogenesis induced by Cardiac shock wave therapy (CSWT) increases myocardial perfusion in endstage CAD patients. Abstract: 70. Jahrestagung der Deutschen Gesellschaft für Kardiologie - Herz und Kreislaufforschung, Mannheim, 15.-17. April 2004.
- Wess, O., Ueberle, F., Dührssen, R.N., Hilcken, D., Krauss, W., Reuner, Th., Schultheiss, R., Staudenraus, I., Rattner, M., Haaks, W., Granz, B. Working Group Technical Developments - Consensus Report. In: Chaussy, C., Eisenberger, F., Jocham, D., Wilbert, D. (eds.) High Energy Shock Waves in Medicine. Georg Thieme Verlag, Stuttgart 1997.
- Delius, M., Draenert, K., Diek, Al., Draenert, Y. Biological effects of shock waves: in vivo effect of high energy pulses on rabbit bone. Ultrasound Med. Biol. 21:1219, 1995.
- Forssman, B., Hepp, W.: Stosswellen in der Medizin, Medizin in unserer Zeit 4 :10, 1980.
- Church, C. A theoretical study of cavitation generated by an extracorporeal shock wave lithotripter. J. Acoust. Soc. Am. 86:215, 1989.
- Crum, L.A., Cavitation on microjets as a contributory mechanism for renal calculi disintegration in ESWL. J. Urol. 140: 1587, 1988.
- Wess, O. Hypothesis Towards Associative Pain Memory and Pain Management by Shock wave Thereapy. Abstract: Seventh Congress of the International Society for Musculoskeletal Shockwave Therapy. Kaohsiung/Taiwan, 1.-4. April, 2004.
- Gleitz, M., Die Bedeutung der Trigger-Stosswellentherapie in der Behandlung pseudoradikulärer Cervicobrachialgien. Abstracts 53. Jahrestagung der Vereinigung Süddeutscher Orthopäden e.V., Nr. 328, April 2005.

REPRINT REQUEST AND CORRESPONDENCE TO:

Dr. Othmar Wess
Physicist
Director Product Development/Marketing
STORZ MEDICAL AG
Unterseestrasse 47
CH-8574 Kreuzlingen
Switzerland
Tel.: +41-71-677 4545
Direct +41-71-677 4525
Fax +41-71-677 4509
e-mail: wess.othmar@storzmedical.com

Extracorporeal Shock Wave Therapy (ESWT) in Skin Lesions



W. Schaden

R. Thiele

C. Köpl

A. Pusch



Introduction

Since 1981 extracorporeal shock waves have been used very successfully for the disintegration of calcified deposits in urology as well as in orthopedics. Due to high efficacy and few side effects, this therapy soon becomes very popular around the world. Since 1990 (1) shock waves have also been used for a variety of orthopedic indications. The therapy proved effective for tendon insertion conditions such as fasciitis plantaris (heel spur) and calcific tendinitis of the shoulder. Shock wave therapy is also widely used for lateral epicondylitis (tennis elbow) as described within previous chapters. Due to the few side effects shock waves also gain ground for the treatment of pseudoarthrosis (non union) and delayed union. Non-invasive and without clinical significant side effects, ESWT has also been used successfully in pilot studies for the treatment of osteochondritis dissecans (OCD) (2) as well as aseptic bone necrosis (AVN) (3, 4, 12). In Japan, shock waves were used successfully in animal experiments for the treatment of ischemia-induced myocardial dysfunction (5). Even skin flap survival in rats improved as a result of shock wave treatment (6).

When treating septic pseudoarthrosis (osteomyelitis), often linked to skin lesions (fistula formation, skin defects, Ö), bone tissue would consolidate and skin defects would heal particularly fast in many cases. In addition, Gerdsmeyer (7) found in vitro bactericidal effect of shock wave therapy. Encouraged by such findings, a pilot study on the treatment of skin lesions with ESWT was conducted.

Material and Methods

To conduct the study an OrthoWave 180c from MTS was used. Since most often surface defects are involved, the shock wave head was modified in that the shock wave would no longer be focussed but be roughly plane to the treatment area. Low energy flow densities were used to treat the skin lesions. Depending on the size of the defect, the number of impulses varied from a few 100 to several 1,000. No anesthesia was necessary due to the defocussing and low energy of the shock waves. In principle, the treatment was performed as an outpatient except for those patients already admitted for other reasons. Between September 2004 and January 2005, 83 treatments were performed at the Trauma center Meidling Austria on 81 patients

(2 patients were treated in 2 areas). Mean patient age was 61 years. The patient group was made up of 37 women and 44 men. At the same time, 21 patients (13 women and 8 men) were treated at Berlin's Center for Extracorporeal Shock Wave Therapy. The mean age was slightly younger (54 y), The skin pathologies are listed in **Table 1**.

Causes of skin lesions	Number
Posttrauma lesions	44
Postsurgical healing disorders	10
Venous ulcer	25
Arterial ulcer	15
Decubital ulcer	5
Burns	5
Total	104

Since no empiric data were available, treatments were carried out in weekly intervals, in part in biweekly intervals. After the first treatment, the same wound dressing was used in principle as before the shock wave therapy. Only after the second or third treatment when wound conditions had improved, adequate options were indicated.

Results

Table 2 lists the results by lesion cause:

Causes of skin lesions	Number	Healed	>50%	<50%	Dropout
Posttrauma lesions	44 (42%)	39 (89%)	1 (2%)		4 (9%)
Postoperative healing disorders	10 (10%)	10 (100%)			
Venous ulcer	25 (24%)	9 (36%)	8 (32%)	6 (24%)	2 (8%)
Arterial ulcer	15 (14%)	10 (67%)	2 (13%)	1 (7%)	2 (13%)
Decubital ulcer	5 (5%)	4 (80%)			1 (20%)
Burns	5 (5%)	5 (100%)			
Total	104 (100%)	77 (74%)	11 (10%)	7 (7%)	9 (9%)

In the beginning of the treatment, all of the treated skin lesions were to be considered as infected. Particularly striking was a lessening of the infection after the first treatment because of the shock wave related bactericidal effect. None of the patients received any antibiotics. None of the patients experienced any worsening of the wound conditions. Only one (female) patient dropped out after the first therapy because she expected herself to fail. Dropouts involved for the most part very old, in part decrepid patients who, after the improvement of their wound, preferred to avoid the strenuous transportation to the hospital.

Discussion

Based on the initial encouraging results of our pilot study, a completely new potential of shock wave therapy appears to emerge. The patients enrolled in our pilot study are reported as a negative selected patient group because all cases refused to get any surgical intervention. Patients willing to get surgery were referred to and shock wave therapy was not offered. The promising outcome after this non-invasive treatment option in chronic wound care justifies to indicate shock wave in those soft tissue conditions as described above. For sure further studies have to be performed to determine optimum treatment parameters. Finally subsequent prospective, randomized controlled double-blind studies may demonstrate the efficacy and safety of ESWT in treating skin lesions.

Literature

1. Haupt G, Haupt A, Gerety B, Chvapil M., Enhancement of fracture healing with extracorporeal shock waves. AUA Annual Meeting, New Orleans 1990.
2. Thiele R., Marx S., Ludwig J., Herbert Chr. Extracorporeal Shockwave Therapy for Adult Osteochondritis dissecans of the Femoral Condyle and the Talus. 7th Congress of the International Society for Musculoskeletal Shockwave Therapy, Kaohsiung April 1-4, 2004.
3. Ludwig J., Lauber S., Lauber J., Hotzinger H.. Shockwave treatment of femur necrosis in the adult. Z Orthop Ihre Grenzgeb. 1999 Jul-Aug; 137(4): Oa2-5. German.
4. Lauber S. High energy extracorporeal shockwave therapy in femur head necrosis. Z Orthop Ihre Grenzgeb. 2000 Sep-Oct; 138(5):Oa3-4. German.
5. Takahiro N., Hiroaki S., Keiji O., Toyokazu U. et al., Extracorporeal cardiac shockwave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo, Circulation; Vol.110: pp 3055-3061, 2004.
6. Meirer R., Kamelger F.S., Huemer G. M., Wanner S., Piza-Katzer H., Extracorporeal shock wave may enhance skin flap survival in an animal model, British Journal of Plastic Surgery, V. 58; pp 53-57, 2005.
7. Gerdesmeyer L., von Eiff C., Horn C., Henne M., Roessner M., Diehl P., Gollwitzer H., Antibacterial effects of extracorporeal shock waves, Ultrasound in Med. & Biol. Vol. 31, pp 115-119, 2005.
8. Wang CJ, Wang FS, Huang CC, Yang KD, Weng LH, Huang HY. Treatment for osteonecrosis of the femoral head: comparison of extracorporeal shock waves with core decompression and bone-grafting. J Bone Joint Surg Am. 2005 Nov;87(11):2380-7. ■

Figure 1 shows the forearm of a 94 year old female patient after a paravenous infusion and a two septic revisions. An abating infection with penicillin-resistant staphylococcus aureus was diagnosed (positive smear test). Because of a chronic COPD the patient is being treated with cortisone. The patient also suffers from chronic lymphatic leukemia. The fist shock wave treatment was applied on 10/13/2004 as an outpatient procedure without anesthetics.



Figure 2 shows the same patient 2 weeks after the first shock wave treatment. A pre-existing therapy with antibiotics was discontinued and the second shock wave treatment (again without anesthetics) was applied.



Figures

Figure 3 shows the lesion of the same patient after the third shock wave treatment on 11/10/2004.



Figure 4 shows the healing status 6 weeks after starting the therapy with altogether 4 shock wave treatments. In total, the 4 treatments lasted just about 12 minutes.



Instructions for Authors

Newsletter of Extracorporeal Shockwave Therapy is an international, peer-reviewed journal produced by International Society for Musculoskeletal Shockwave Therapy (ISMST) and is issued three times a year.

Newsletter of Extracorporeal Shockwave Therapy offers the opportunity to publish original research, clinical studies, review articles, case reports, clinical lessons, abstracts, book reviews, conference reports and communications regarding the scientific or medical aspects of shockwave therapy.

Manuscript Submission

All manuscripts should be sent to the Editor:
By e-mail: prds@uol.com.br
On disk and mail to:
Dr Paulo Roberto Dias dos Santos
Rua Nathanael Tito Salmon, 233
Osasco - São Paulo - Brazil
CEP 06016-075
We encourage authors to submit manuscripts via e-mail. When submitting by e-mail, print mail address and telephone and fax numbers also should be included.

Manuscript Categories

All articles should be well-written in plain English, whereby jargon, acronyms, abbreviations and complicated data should be avoided.

Scientific research:

Theoretical or experimental (basic or applied) scientific research or the practical application of this research. The article should consist of an abstract, key words, introduction, methods, results, discussion, and conclusion.

Length: The manuscript should be no longer than 2,500 words, including title page, abstract, references, legends and tables.

Review articles:

Review articles on topics of general interest are welcomed. Reviews should include the specific question or issue that is addressed and its importance for the shockwave therapy community, and provide an evidence-based, balanced review on this topic. The article should include a description of how the relevant evidence was identified, assessed for quality, and selected for inclusion; synthesis of the available evidence such that the best-quality evidence should receive the greatest emphasis; and discussion of controversial aspects and unresolved issues. Meta-analyses also will be considered as reviews. Authors interested in submitting a review manuscript should contact the editorial office prior to manuscript preparation and submission.

Length: Approximately 2,000 to 2,500 words and no more than 40 references.

Case reports

Authors are encouraged to submit articles with interesting case reports with relevant information regarding diagnosis and therapy, unique for shockwave therapy. The articles should be short, accurate and easy to understand, and should consist of the following:

- A summary with the clinical relevance;

- An introduction explaining the clinical problem;

- A short report of the cases, consisting of history, physical examination, further investigation, treatment and follow-up.

- A discussion, whereby the clinical consequences are described and the most interesting aspects of the case report.

Length: Approximately 750 to 1,200 words and a maximum of 15 references.

Clinical lesson

Authors are invited to give a description and background information of developments in the field of further diagnostics and clinical tests and methods that are relevant to all aspects of shockwave therapy, training and rehabilitation. It is not necessary to include examples of patients, as in case reports. The articles should be up-to-date, short, accurate, and easy to understand and should contain the following:

- A summary with the clinical relevance (max. 150 words)
- And introduction with the theme of the article
- A description of the used test method or diagnostic
- A conclusion with the practical relevance and practical tips.

Length: Approximately 750 to 1,200 words and a maximum of 5 references.

National organisation communications

National organisations are invited to describe any aspect of medical care or science in their country, e.g. the function of their medical committee, medical care of their players, research that is being conducted etc.

Approximately 300 to 500 words

Letters to the editor:

Letters discussing an article that has been published in Journal of Extracorporeal Shockwave Therapy have the greatest chance of acceptance if they are sent in with 2 months of publication. Letters that are approved will be forwarded to the author, who will have 6 weeks to respond. The original letter and the reply will be published simultaneously.

Length: Such letters should not exceed 400 words of text and 5 references. Research Letters reporting original research also are welcome and should not exceed 600 words of text and 6 references and may include a table or figure.

Review of the Literature

Authors are invited to submit summaries of published articles of particular interest for the shockwave therapy community. The opinion of the author should be stated following each summary.

Length: Such a review should be approximately 500 to 700 words. A review of three articles simultaneously should be no longer than 1,000 words.

Conference reports and Abstracts

Authors are invited to submit reports of conferences they have attended, and to include one to three photographs taken at the meetings. Please include the names and highest titles of the persons that can be identified in the photographs. Summaries of work presented at the conference may be submitted for publication as well.

Length: 300 to 500 words per report or abstract.

Manuscript Preparation

Manuscripts should be prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Vancouver Style). http://www.nlm.nih.gov/bsd/uniform_requirements.html

• If submitting by e-mail, text, tables, and figures should be included in the same file. Do not submit duplicate copies by mail or fax.

• Articles should be in Microsoft Word format.

• Double-space throughout, including title page, abstract, text, acknowledgements, references, figure legends, and tables.

• Do not use abbreviations in the title or abstract and limit their use in the text.

• Please use Times New Roman, size 12.

• On the title page include the full names, highest academic degrees, and affiliations of all authors. If an author's affiliation has changed since the work was done, list the new affiliation as well.

• Figures, summary tables and diagrams should be numbered consecutively throughout the paper. Photographs should be clearly labelled.

• References. Number references in the order they appear in the text; do not alphabetise. In text, tables, and legends, identify references with superscript Arabic numerals. When listing references, follow AMA style and abbreviate names of journals according to Index Medicus. List all authors and/or editors up to 6; if more than 6, list the first 3 followed by et al.

- Journal: Kibler WB. The role of the scapula in athletic shoulder function. Am J Sports Med. 1998;26(2):325-337.

- Book: Perry J. Biomechanics of the shoulder. In: Rowe CR, ed. The shoulder. London: Churchill Livingstone, 1988:1-15.

• Footnotes should be avoided.

Review process

Contributions will be reviewed by the editorial board for scientific research, review papers, case reports, clinical lessons, and abstracts. Manuscripts should meet the following criteria: material is original; writing is clear; study methods are appropriate; the data are valid; conclusions are reasonable and supported by the data; information is important; and topic has general shockwave therapy interest.

Manuscripts with insufficient priority or quality for publication are rejected promptly. Other manuscripts are sent to expert consultants for peer review. Peer reviewer identities are kept confidential, but author identities are known by reviewers. The existence of a manuscript under review is not revealed to anyone other than peer reviewers and editorial staff.

Intellectual property

• The article must be your own original work.

• If the article contains any photographs, figures, diagrams, summary tables, graphs or other non-textual elements that are not your own original work, you must ensure that you have obtained written permission from the copyright owner to include their work in your article for publication in Journal of Extracorporeal Shockwave Therapy. Permission letters must be submitted with your article.

DUPLO PODER

ARCOXIA*

(ETORICOXIBE), MSD



PODER rápido e prolongado

Em um estudo clínico de odontalgia pós-operatória realizado com ARCOXIA 120 mg[†]

O início da analgesia
começou já aos
24 minutos

24 minutos,
início da ação¹

24x24
horas,
duração da ação¹



O efeito analgésico persistiu por até 24 horas

[†] ARCOXIA 120 mg só deve ser utilizado durante o período sintomático agudo.

Referência bibliográfica: 1. Malmstrom K, Sapre A, Coughlin H et al. Etoricoxib in acute pain associated with dental surgery: A randomized, double-blind, placebo- and active comparator-controlled dose-ranging study. *Clin Ther* 2004;26(5):667-679.

Resumo do estudo: estudo com distribuição randômica, de grupos paralelos, que envolveu 398 pacientes com dor moderada a intensa após extração de, pelo menos, dois terceiros molares. Os pacientes receberam uma dose única de 60 mg, 120 mg, 180 mg ou 240 mg de ARCOXIA, 400 mg de ibuprofeno e placebo. Os pacientes interromperam dois cronômetros durante o tratamento: quando alcançavam alívio perceptível da dor e quando alcançavam alívio significativo da dor. A intensidade e o alívio da dor foram medidos já 15 minutos após a administração da dose. O início da analgesia ocorreu já 24 minutos após a dose em pelo menos 50% dos pacientes tratados com 120 mg de ARCOXIA e a analgesia persistiu por até 24 horas após a dose em 72% dos pacientes tratados com essa dose; as doses mais altas de ARCOXIA não proporcionaram nenhum efeito clínico adicional.

ARCOXIA (etoricoxibe), MSD. INDICAÇÕES: tratamento agudo e crônico dos sinais e sintomas da osteoartrite e da artrite reumatóide, da gota aguda e da dismenorria primária; alívio da dor aguda e crônica. **CONTRA-INDICAÇÃO:** hipersensibilidade a qualquer componente do produto, insuficiência cardíaca congestiva (NYHA II-IV), doença cardíaca isquêmica e/ou doença cerebral vascular estabelecida (incluindo pacientes recentemente submetidos à cirurgia de revascularização do miocárdio ou angioplastia). **PRECAUÇÕES:** Como os riscos cardiovasculares dos inibidores seletivos da ciclooxigenase-2 podem aumentar com a dose e a duração da exposição, deve-se usar a menor dose efetiva diária pelo período de tempo mais curto possível. Pacientes com fatores de risco significativos para eventos cardiovasculares (p. ex., hipertensão, hiperlipidemia, diabetes mellitus, tabagismo) ou doença arterial periférica devem ser tratados apenas com o etoricoxibe após criteriosa consideração. ARCOXIA não é recomendado para pacientes com doença renal avançada; se o tratamento for necessário, recomenda-se monitorização rigorosa da função renal desses pacientes. Deve-se ter cautela ao iniciar o tratamento com ARCOXIA em pacientes com desidratação considerável e considerar a possibilidade de retenção hídrica, edema ou hipertensão quando ARCOXIA for utilizado em pacientes com edema, hipertensão ou insuficiência cardíaca preexistentes. Os médicos devem estar cientes de que determinados pacientes, especialmente aqueles com mais de 65 anos de idade, podem desenvolver úlceras(s) no trato gastrointestinal superior, independentemente do tratamento. Em caso de disfunção hepática persistente, ARCOXIA deve ser descontinuado. ARCOXIA deve ser utilizado com cautela por pacientes que já tenham apresentado crises agudas de asma, urticária ou rinite causadas pelo uso de salicilatos ou inibidores não específicos da ciclooxigenase. ARCOXIA pode mascarar a febre que constitui um sinal de infecção. **Gravidez:** categoria de risco C. ARCOXIA só deve ser usado durante os dois primeiros trimestres da gravidez se o benefício potencial justificar o possível risco para o feto. Não se sabe se ARCOXIA é excretado no leite humano; por isso, quando ARCOXIA for administrado a nutrízes deve-se considerar a importância do medicamento para a mãe ao se decidir entre descontinuar a amamentação ou a medicação. A segurança e a eficácia em pacientes pediátricos não foram estabelecidas e, em geral, não foram observadas diferenças no perfil de segurança e na eficácia do medicamento entre pacientes idosos (65 anos de idade ou mais) e pacientes mais jovens. **INTERAÇÕES MEDICAMENTOSAS:** **Warfarina:** a administração de 120 mg de ARCOXIA uma vez ao dia foi associada com aumento no tempo de protrombina de aproximadamente 13% (*International Normalized Ratio - INR*). **Ritampicina:** ocorreu redução de cerca de 65% das concentrações plasmáticas do etoricoxibe quando este foi administrado com a rifampicina. **Meloxicam:** doses de 60 mg e 90 mg ao dia de ARCOXIA durante 7 dias não exerceram efeito na concentração plasmática ou na depuração renal de 75 mg e 20 mg de meloxicam em doses únicas semanais para o tratamento da artrite reumatóide. Em um estudo, a dose de 120 mg de ARCOXIA aumentou a concentração plasmática do metotrexato em 28% e reduziu a depuração renal do metotrexato em 13%; por isso, deve-se monitorar a toxicidade relacionada ao metotrexato quando forem administradas doses maiores que 90 mg de ARCOXIA ao dia com essa medicação. **Inibidores da ECA:** relatos sugerem que pode haver diminuição dos efeitos anti-hipertensivos dos inibidores da ECA quando ARCOXIA for administrado com essas medicações. **Lítio:** relatos sugerem que pode haver aumento dos níveis plasmáticos de lítio quando ARCOXIA for administrado com lítio. **Ácido acetilsalicílico em baixas doses:** pode ser utilizado concomitantemente a ARCOXIA; este, porém não exerce efeitos sobre as plaquetas e não substitui o ácido acetilsalicílico para profilaxia cardiovascular. **Anticoncepcionais orais:** a administração concomitante de ARCOXIA e um contraceptivo oral com etinilestradiol aumentou a concentração plasmática do etinilestradiol em 37% a até 60%. Um aumento na exposição ao etinilestradiol pode aumentar a incidência de eventos adversos associados aos contraceptivos orais. **REAÇÕES ADVERSAS:** as seguintes experiências adversas relacionadas à medicação foram relatadas (incidência e $\geq 1\%$) em estudos clínicos de 12 semanas sobre osteoartrite, artrite reumatóide ou dor lombar crônica: astenia/fadiga, tontura, edema de membros inferiores, hipertensão, dispnéia, prurido, náuseas, cefaléia e aumento de ALT e AST. O perfil de experiências adversas relatadas nos estudos sobre gota aguda e analgesia aguda foi similar ao relatado nos estudos combinados de osteoartrite, artrite reumatóide e dor lombar crônica. **POSOLOGIA:** Osteoartrite: 60 mg uma vez ao dia. Artrite reumatóide: 90 mg uma vez ao dia. Gota aguda: 120 mg uma vez ao dia (somente durante o período sintomático agudo e por não mais que 8 dias). Dor aguda e dismenorria primária: 120 mg uma vez ao dia (somente durante o período sintomático agudo). Dor crônica: 60 mg uma vez ao dia. (Doses maiores que as recomendadas para cada indicação ou não apresentaram eficácia adicional ou não foram estudadas; portanto, as doses acima são as doses máximas recomendadas.) **Insuficiência hepática:** em pacientes com insuficiência hepática leve (escore de Child-Pugh 5-6), a dose de 60 mg uma vez ao dia não deve ser excedida. Em pacientes com insuficiência hepática moderada (escore de Child-Pugh 7-9), não deve-se exceder a dose de 60 mg em dias alternados. Não há dados clínicos ou farmacocinéticos em pacientes com insuficiência hepática grave (escore de Child-Pugh ≥ 10). **Insuficiência renal:** o tratamento com ARCOXIA não é recomendado para pacientes com doença renal avançada (clearance de creatinina <30 ml/min). Não há necessidade de ajuste posológico para pacientes com insuficiência renal leve/moderada (clearance de creatinina ≥ 30 ml/min). **REGISTRO MS:** 1.0029.0035. **VENDA SOB PRESCRIÇÃO MÉDICA.**

Nota: antes de prescrever ARCOXIA, recomendamos a leitura da Circular aos Médicos (bula) completa para informações detalhadas sobre o produto.

MERCK SHARP & DOHME
MC 078/06 01-2007-ACX-06-BR-078-J

www.msdonline.com.br

* Marca depositada no INPI em 31 de janeiro de 2001 por Merck & Co., Inc., Whitehouse Station, NJ, EUA.

on line
0800-012-22-32
E-mail: arcoxia@msd.com.br
www.msdonline.com.br