

# Extracorporeal Shock Wave Therapy: Theory and Equipment

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Shock waves were employed for many years for the management of uroliths in people, but in the 1990s use was extended to musculoskeletal diseases. Much is known about the physics of shock waves and shock wave generators. Less is known about the mechanisms of action of shock waves in musculoskeletal diseases in people or horses. This chapter describes the shock wave itself, how shock waves are generated, and what is known about shock waves and interactions with musculoskeletal tissues.

**Key Words:** Extracorporeal shock wave therapy, equine, musculoskeletal disease.

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## Definition of a Shock Wave

Shock waves appear in many forms and various media. A commonly known shock wave is the thunder following lightning. Shock waves are also associated with earthquakes and volcanic eruptions. In general, a shock wave is the result of a sudden release of chemical, electrical, nuclear, or mechanical energy. The shock waves used for medical applications are transient pressure disturbances propagated rapidly in 3-dimensional space or are sharp, thin fronts through which there exists a sudden change in pressure.<sup>1</sup>

Typical characteristics of shock waves include a short rise time on the order of a few nanoseconds reaching a peak pressure of up to 100 MPa or 1,000 times atmospheric pressure (Fig 1). After the rapid increase of pressure there is a longer period of decreasing pressure. Pressure returns to normal and then becomes negative; negative pressure is one of the hallmarks of a shock wave, on the order of 10% of the maximum positive pressure, and may cause cavitation effects. For medical purposes, for extracorporeal shock wave lithotripsy (ESWL) in urology or for extracorporeal shock wave therapy (ESWT) in orthopedics, the shock waves are generated outside the patient's body and focused on the target, the urolith or the orthopedic indication.

A number of parameters are used to describe shock waves. The energy of the shock wave ( $E$ ) is measured in millijoules (mJ). The total energy is determined by:  $E = [A-\rho c] \int p^2(t) dt$ , where the integral is the area under the curve  $p$  squared (Fig 1), the area of the wave surface is  $A$ , the density of the medium is  $\rho$ ,

the propagation speed in the fluid is  $c$ , and  $t$  is time. This formula defines the total energy contained in a shock wave, without explaining, however, whether this energy is concentrated on a small area (focus) or spread over a large surface. Therefore, additional parameters for describing the focus are necessary (Fig 2).

A common parameter to describe shock waves is the energy flux density (EFD), also referred to as energy density. It is the amount of energy per unit area and is defined by the energy as calculated above, divided by the area of the wave surface:  $EFD = [E-A] = [1-\rho c] \int p^2(t) dt$ . The energy density is the amount of energy in one square millimeter of the focal point field and is measured in mJ/mm<sup>2</sup> and can be up to 2.26 mJ/mm<sup>2</sup>.<sup>2</sup> When the same amount of energy is deposited at a small focal point it will have a greater energy density than when there is a larger focal point. Energy and EFD can be calculated for the positive part of the shock wave ( $E_+$ ,  $EFD_+$ ) as well as the sum of the positive and negative parts ( $E_{tot}$ ,  $EFD_{tot}$ ). The total energy in a shock wave is the energy flux density integrated over the entire shock wave field. The total energy applied during therapy is the total energy per pulse multiplied by the number of pulses.

## Acoustic Impedance

Shock waves are initiated by the deposition of energy into a fluid media. The fluid media is similar in acoustic impedance to soft tissues in the body. When the wave generator is coupled to the skin by an acoustic coupling media the generated wave can continue into the tissue. In the formulas above the tissue density multiplied by the velocity of sound in tissue ( $\rho c$ ) represents the tissue properties and the product is the acoustic impedance ( $Z$ ) of the tissue.

Shock waves can propagate through tissues of similar acoustic impedance without significant energy loss. The acoustic impedance of fat, muscle, and water are similar whereas there is a large difference to the impedance of air, lung tissue, bone, and kidney stones (Table 1). At small differences of the acoustic impedance only small amounts of energy are lost due to reflection or absorption. The ratio of reflected and transmitted intensity is given by  $EFD_{reflected} = EFD_{in} (Z_2 - Z_1 / Z_2 + Z_1)$ , and the transmitted energy is  $EFD = EFD_{in} 4(Z_2 Z_1 / Z_2 + Z_1)^2$ . Using these equations, Table 2 provides the amount of reflected and transmitted intensity of a plane wave traveling through water and impacting tissue.

Much of the shock wave is reflected by lung tissue (Table 2). The reflected wave changes phase by 180° when hitting a surface of lower acoustic impedance that results in a strong tensile wave. Tensile waves can cause cavitation effects and have strong disruptive potential creating the possibility of damage to pleural or intestinal surfaces.

In vivo, in bone, at the energy levels used, shock wave ther-

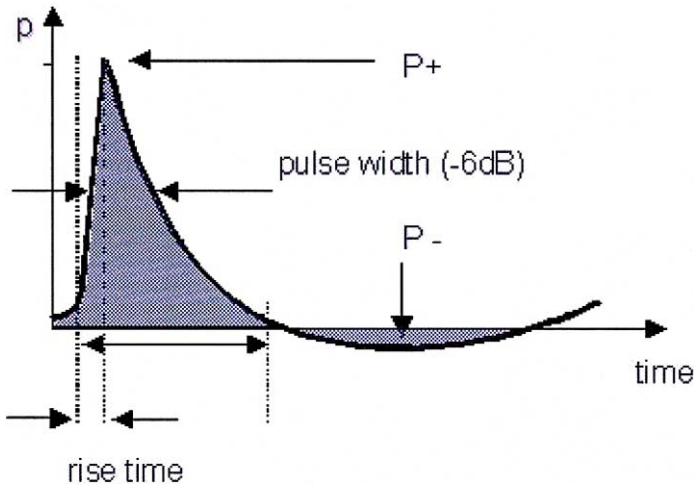
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**Fig 1.** The pressure (y axis) and time (x axis) measurements of a shock wave. The rise time is 5 to 10 ns with the entire positive wave within a microsecond. The maximum positive pressure ( $P_+$ ) is the highest pressure amplitude of the shock wave. The  $-6$  dB pulse width is the time during which the pressure is higher than 50% of  $P_+$ . The shaded area under the curve represents the total positive and negative energy of the shock wave.

apy does not result in fragmentation, but the energy has other effects. Acoustic impedance must be considered when a clinician is planning shock wave therapy. For example, it is not possible for shock waves of significant energy to penetrate the hoof wall, even after soaking in water for multiple days (McClure SR, unpublished data, 2002). Additionally, since minimal

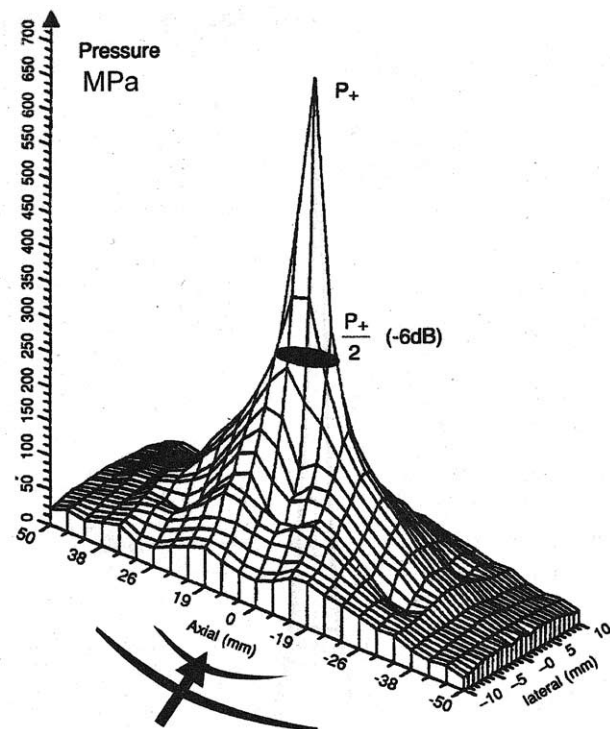
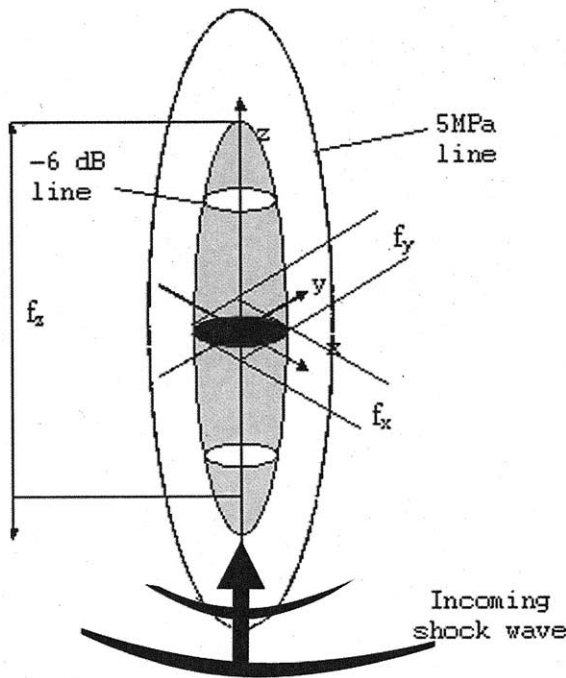
energy is completely transmitted through bone the treatment site should be between the skin surface and the near cortex.

### Compression/Tension/Cavitation

As a pressure wave propagates through tissue it is initially under compression, but as the wave front moves on, a negative component is present and the tissue is under tension. This effect is mechanically advantageous, resulting in fragmentation of uroliths. A phenomenon that occurs with shock waves is the development of cavitation bubbles. Cavitation occurs when there are microheterogeneities in liquids such as free gas, solid particles, or combinations of these serve as cavitation nuclei.<sup>3</sup> When the tension portion of the shock wave hits gas nuclei they grow, forming a cavitation cluster. The shape and dynamics are determined by the distribution of initial sizes of the nuclei, the characteristics of the tension portion of the shock wave, and the boundary conditions. The boundary conditions are the surroundings of the media where cavitation occurs. The boundary conditions are different in a test tube, near a kidney stone, or in an infinite space. This will result in differences in sizes and number of cavitation bubbles in different environments.

A second cavitation effect is shock wave-gas bubble interaction during the positive pressure portion of the shock wave. The shock wave deforms the walls of a preformed stationary gas bubble, and at the point of impact, a water jet originates in the direction of the shock wave.<sup>4</sup> The generated water jets are faster and more damaging than are the jets from collapse of a cavitation bubble.<sup>5</sup>

Cavitation bubbles can be seen in a water bath when aluminum foil is placed in the propagation path of the shock waves.



**Fig 2.** As the shock wave converges it forms a 3-dimensional pressure front. On the left is a schematic of the focal point showing pressure and area, and on the right is a 3-dimensional surface plot. Within the pressure wave front there are defined areas where the pressure exceeds specific points. The focal size ( $f_x$ ,  $f_y$ ,  $f_z$ ) represents the diameter and length of the focal zone at the  $-6$  dB zone or the 5 MPa zone, which are commonly used. The  $-6$  dB zone is the volume of tissue, where the pressure is at least one-half of the peak pressure. The 5 MPa area is the area in which the pressure exceeds 5 MPa. The dimensions of the ellipsoid are dependent on the specific focusing mechanism of the generator and the type of shock wave generator. A shock wave generator that precisely focuses the wave will result in a smaller  $f_x$ ,  $f_y$ ,  $f_z$  and therefore a higher energy per unit area (EFD). The solid black ellipse in both figures represents the same area of the wave.

**TABLE 1. Acoustic Impedance of Tissues**

	Sound Velocity [m/s]		Specific Density [%/cm <sup>3</sup> ]	Acoustic Impedance [kg/s · m <sup>2</sup> ]*10 <sup>-6</sup>	
	Min	Max		Min	Max
Lung	650	1160	0.4	0.260	0.464
Fat	1476		0.928	1.370	
Air	330	343	0.0013	0.000429	0.000446
Water	1492		0.998	1.489	
Kidney	1570		1.04	1.633	
Muscle	1545	1630	1.06	1.638	1.728
Bone marrow	1700		0.97	1.649	
Bone	2700	4100	1.8	4.860	7.380
Kidney stone	4000	6000	1.9-2.4	7.600	14.400
Iron	5100	5800	7.9	40.290	45.820

The sound velocity and specific density are used to calculate the acoustic impedance for each material. The acoustic impedance determines how well the shock wave is transmitted through a material or how much energy is dissipated within the tissue.

The primary bubble can have a size of 5 to 7 mm, 500 μs after the shock wave has passed. A second bubble oscillation follows during the next millisecond. At the foil surface, many small bubbles can coalesce to form a larger bubble and collapse within milliseconds. Gas can, however, diffuse into bubbles during the expansion phase. Low internal pressure within the bubble may lead to gas accumulation.<sup>6</sup> Cavitation bubbles with a radius of up to 40 μm remain in place for at least 1 s after a 100 MPa shock wave is passed through a water tub.<sup>4</sup>

There is only limited information about the development of cavitation bubbles within tissue. Ultrasonographic examination revealed the presence of cavitation bubbles when shock waves were applied to pig liver.<sup>7</sup> Cavitation was associated with damage to liver cells.<sup>8</sup> Delius and colleagues<sup>7</sup> found tissue damage at the exact sites where the ultrasound signals from cavitation were picked up. Cavitation potentially causing tissue damage was identified in renal tissue.<sup>9,10</sup> When shock waves were propagated through blood, no cavitation bubbles were found.<sup>11</sup> There is little known about cavitation from shock waves within other body tissues.

### Physical Behavior of Shock Waves

Shock waves are subject to reflection, diffraction, dissipation, and absorption and not all shock waves reach the focal point. The effects of reflection, diffraction, refraction, scattering, and attenuation for shock waves are similar to the effects for light propagation. The basic refraction formula is  $(\sin\alpha/\sin\beta) = (n_1/n_2)$ , where  $\alpha$  and  $\beta$  are the angle of incidence and the angle of reflection respectively,  $n_1$  and  $n_2$  are the optical refraction indices. For shock waves, the optical refraction indices are replaced by sound velocity  $c$  of the 2 media and the modified formula is  $(\sin\alpha/\sin\beta) = (c_1/c_2)$ . A sound wave passing water–muscle tissue boundary at an angle of incidence of 10° will be diffracted to an angle of 9.1° to 9.7°, depending on the muscle tissue density, which determines the sound velocity in the tissues. Deflection, therefore, plays a minor role when a shock wave travels from the water-filled probe into the body. Within the body the deflection angles are dictated by the number of interfaces with different sound velocities in the path of the shock wave.

For larger angles of incidence only a minor part of the incoming shock wave will travel through the boundary. A single simple method for analyzing the reflection of waves obliquely incident on the surface of a solid is not available. Because of

differences in porosity and internal elastic structure of various tissues, the nature of the transmitted shock wave varies widely.

A major effect of a wave that is only partly reflected is absorption. Absorption of acoustic waves occurs in tissues with pores and cavities. Absorption occurs from friction of the propagating shock wave on the walls of tissue pores and much of the acoustic energy is converted to heat. Tissues that are efficient for acoustic absorption are porous tissues that have open spaces. For example, shock waves are absorbed quickly in cancellous bone but are propagated well in cortical bone.

Total attenuation of an acoustic wave includes energy loss (absorption) and tissue scattering. For most soft tissues, scattering is negligible and attenuation and absorption coefficients are approximately equal.<sup>12</sup> In contrast, lung tissue has the highest attenuation coefficient of any tissue and the attenuation comes almost entirely from scattering. Furthermore, at a frequency of 1 MHz, bone has the highest true absorption of the body tissues, more than 20 times higher than any soft tissue.<sup>12</sup>

All of the previously mentioned effects occur in vitro as well as in vivo.<sup>13</sup> In tissue, the shape of shock waves changes very little compared with measurements done in water. The peak pressure dropped to 70% and the focal zone became wider and longer by 40% and 60%, respectively. When compared with water, the rise time of a shock wave in tissues was slower by up to 100 ns because of higher absorption.

Acoustic waves can dislocate cells. For example, an ultrasound transducer of 300 kHz and 10 W/cm<sup>2</sup> produces sound waves that generate a displacement amplitude of 0.2 μm. While the magnitude of displacement is a small fraction of the size of a cell, the resultant acceleration is 70,000 times greater than the acceleration from gravity.<sup>14</sup> With shock waves, cell displacement occurs without tissue heating. A shock wave, with a duration of 10 μs and an energy flux density of 0.15 mJ/mm<sup>2</sup> generates a comparable power density of 1,500 W/cm<sup>2</sup>. The high intensity only occurs during the 10-μs pulse duration, resulting in a signal-to-pause ratio, at a typical pulse repetition rate of 4 Hz, of 1:25,000. This average intensity is well below the widely accepted intensity 0.1 W/cm<sup>2</sup> level of where tissue heating occurs.

### Mechanisms to Generate a Shock Wave

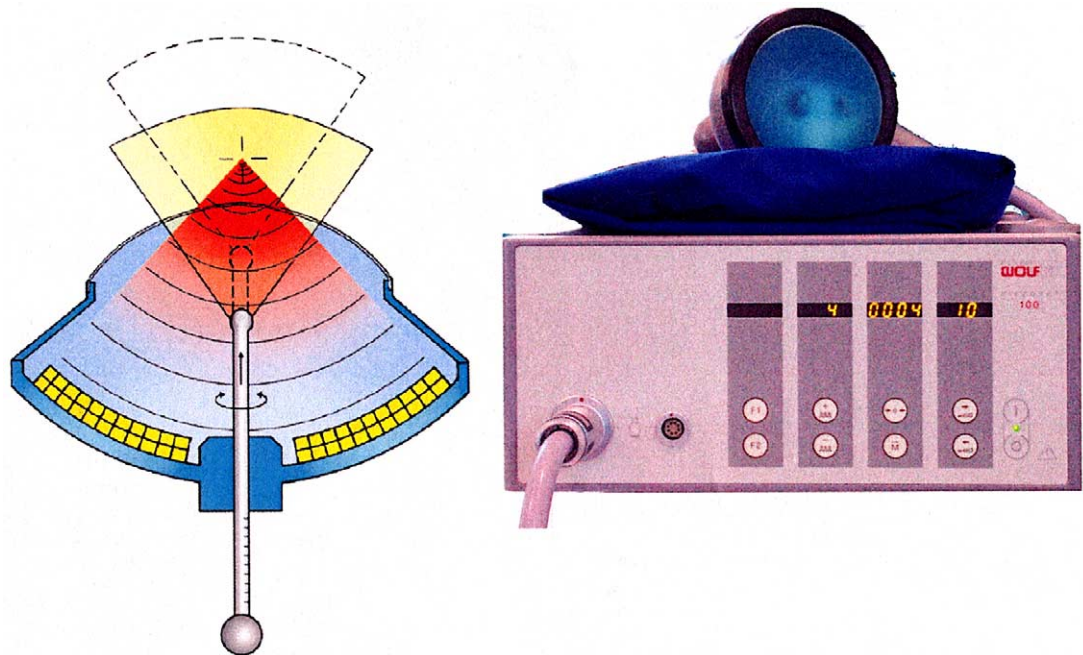
The acoustic impedance of water and soft tissue are similar. Since there is a negligible amount of reflected intensity of a shock wave

**TABLE 2. Effect of the Tissue on the Shock Wave**

Tissue	EFD <sub>reflected</sub> (%)		EFD <sub>transmitted</sub> (%)	
	From	to	From	To
Lung	49	28	51	72
Fat	0.2		99.8	
Air	99.9		0.1	
Water	0		100	
Kidney	0.2		99.8	
Muscle	0.2	0.6	99.8	99.4
Bone marrow	0.3		99.7	
Bone	28	44	72	56
Kidney stone	45	66	55	34
Iron	86	88	14	12

The calculated ratios of transmitted and reflected energy of a plane wave front traveling from water to the materials shown in a 90° angle by using the two formulas for EFD<sub>reflected</sub> and EFD<sub>transmitted</sub>. Within the body, shock waves travel well through soft tissue (muscle, fat, and kidney) to the desired treatment area such as bone or a kidney stone.

Fig 3. Piezoelectric crystals expand or contract rapidly depending on polarity when high voltage is applied. A pressure wave can then be generated. In piezoelectric shockwave transducers several crystals in a single- or double-layer arrangement can be used. Here, the Wolf piezoelectric generator has a double layer of piezo crystals. The probe in the center is used to focus the shock wave at the desired depth. This is a portable machine with a handheld probe.

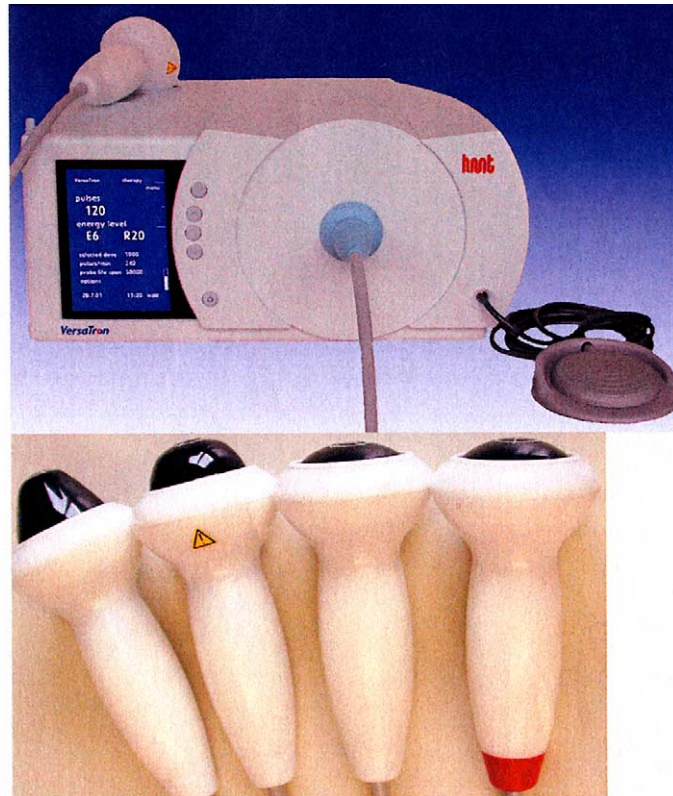
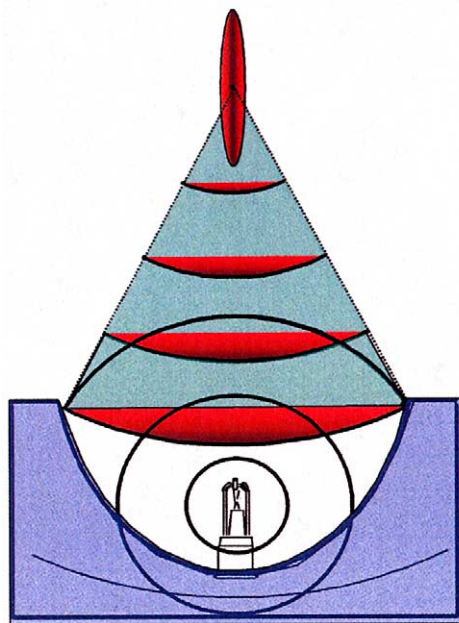


traveling from water into tissue, the shock waves for medical purpose are generated in water. There are several methods to generate a shock wave in water. Originally, shock waves were generated by dropping an explosive pellet into fluid. However, shock waves generated by this method were inconsistent and this method fell out of favor. For clinical applications electricity is used as an energy source to generate shock waves.

There are 3 mechanisms to generate a focused shock wave, that is, piezoelectric, electromagnetic, and electrohydraulic (Figs 3, 4, and 5). These mechanisms generate focused shock waves by conversion of electricity into rapid physical movements within fluid. Each mechanism uses a capacitor, which is charged at different voltages and then rapidly discharged within the acoustic transducers.



Fig 4. The electromagnetic generators have a mechanism similar to a loudspeaker. The electrical capacitor is discharged through a flat coil generating a rapidly changing magnetic field. This magnetic field induces an opposing magnetic field in a metal membrane above the coil, causing a repulsive force and rapid movement of the membrane. A special type of the electromagnetic transducer by one manufacturer uses a cylindrically shaped coil and membrane generating a radial movement of the membrane. The electromagnetic transducers are often referred to as EMSE systems (EMSE = electromagnetic shockwave emitter). When the coil moves outward, the pressure wave (arrows) is reflected to the focal point. The Storz Minilith with an inline ultrasound for focusing is shown. The generator head is on a flexible arm.



**Fig 5.** The electrohydraulic or spark gap principle uses a high voltage applied across 2 electrode tips submerged in a fluid media. The powerful discharge creates a rapidly expanding plasma bubble between the tips. The surrounding water slows the expansion of the bubble. A shock front is emitted from the plasma bubble surface as soon as the expansion velocity drops below sound velocity. An almost spherical-shaped undisturbed shock front is formed. The ellipsoidal reflector focuses the wave to the focal point. The electrohydraulic principle was first used in a lithotripter in the early 1980s for medical applications. Electrohydraulic generators have been rapidly developed in a few years, overcoming this disadvantage of low electrode lifetime. The HMT VersaTron (shown) is a portable handheld system. The depth is controlled by selecting the appropriate hand piece, ranging from 5, 20, 35, and 80 mm (left to right).

### Focusing the Shock Wave

Importantly, shock waves are modified for medical use by forming a convergent wave. Convergent waves have a weak pressure surface but concentrated energy. By using convergent waves the clinician can achieve the desired effect without causing significant side effects (eg, disintegration of a kidney stone without causing damage to the kidney itself).

Shock waves can be focused by different methods. The piezo crystals of piezoelectric systems are arranged like a sphere cap with the focal zone in the center of the sphere. The flat electromagnetic generator uses an acoustic lens to focus the emitted waves. The cylindrical electromagnetic system employs a parabolic reflector, which focuses the cylindrically shaped wave front to a focal spot. Finally, the electrohydraulic systems use a metal half-ellipsoid with this system; the electrode, which sits in the first focus of the ellipsoid, emits the spherical shock wave front that is then reflected at the metal part of the ellipsoid (Figs 3, 4, and 5).

Once a shock wave is focused there must be a mechanism to direct it at the treatment site. For instance, lithotripsy depends on precise focusing to direct the energy to the urolith. The original equipment depended on fluoroscopy for imaging. To reduce radiation exposure ultrasonographic equipment was then developed for continual, real-time monitoring. Focusing is important for musculoskeletal applications, but precision is considerably less than that required for treatment of uroliths. Ultrasonographic and fluoroscopic devices are used with some

equipment, but since single-dimension focusing is adequate for most musculoskeletal applications, simple mechanisms to measure depth have been incorporated into some machines.

A 3-dimensional, cigar-shaped focal zone is characteristic of each type of shock wave generator (Fig 2). Piezoelectric systems usually have a small focal zone, but the focal zone of electrohydraulic systems is large and increases in size when high powers are used. The maximum pressure and EFD of piezo systems are higher than compared with that of other generators.

To compare shock wave generators, numerous parameters are used. Unfortunately, until the mechanisms that create desired outcomes of shock wave therapy are understood, important parameters of the generators cannot be understood. Nonetheless, the industry has agreed on a set of parameters used to compare devices for orthopedic use<sup>b</sup> (Table 3). A parameter set for shock wave description has been established in 1997 by the scientific advisory board of the DIGEST, German and International Society for Extracorporeal Shock Wave Therapy. The scientific advisory board consists of physicists and engineers who have been involved in the science and development of shock wave technology for medicine for years. Information, in German, at <http://www.digest-ev.de>. Information about all parameters for all devices is published by the DIGEST at: <http://www.stosswellentherapie.net/fach/index.html>.

While methods used to compare devices are standardized, the actual values listed for each device are provided by the manufacturer.

**TABLE 3. Selection of Commonly Used Parameters for Focused Shock Wave Generators**

Physical Parameter	Unit	At Device Minimum Power Setting	At Device Medium Power Setting	At Device Maximum Power Setting
Positive peak pressure $P_+$	MPa	5.5-40.6	14.2-61	25.6-140.2
-6 dB focal size $f_x$ (-6 dB)	mm	2.8-21.8	2.1-23	1.3-26
$f_y$ (-6 dB)	mm	2.8-21	2.1-23.6	1.3-25.5
$f_z$ (-6 dB)	mm	10.2-103	6.4-92	4.2-96
5 MPa focal size lateral $f_{x,y}$ (5 Mpa)	mm	2.2-33	7.8-42	11.9-58
Positive energy flux density EFD $_+$	mJ/mm <sup>2</sup>	0.02-0.13	0.09-0.73	0.12-1.67
Total energy flux density EFD	mJ/mm <sup>2</sup>	0.04-0.15	0.13-1	0.15-2.26
Positive energy in -6 dB focus E $_+$ (-6 dB)	mJ	0.38-9.6	1.22-65.8	1.66-145
Total energy in -6 dB focus E (-6 dB)	mJ	0.7-9.6	2.17-65.8	2.3-145
Positive energy in 5 MPa focus E $_+$ (5 MPa)	mJ	0.5-18.1	1.8-99.3	6.5-226.2
Total energy in 5 MPa focus E (5 MPa)	mJ	1.6-22.2	4.8-160	7.7-296.2
Positive energy in 5 mm focus E $_+$ (5 mm)	mJ	0.3-2.5	1.3-10.7	1.99-25.7
Total energy in 5 mm focus E (5 mm)	mJ	0.45-3.7	1.86-12.03	2.26-33

Selected parameters from all of the focused shock wave therapy systems currently available including all 3 of the shock wave generating mechanisms are given. The minimum and maximum for each category are shown. The parameter range for the different devices is large; most differ by 1 order of magnitude or more.

### Coupling

While early machines had a patient submersion system, modern-day “dry” shock wave generators are equipped with fluid-filled heads that have a silicone-type membrane. To limit changes in acoustic impedance during energy transfer from the generator to the patient, hair should be removed and air must be displaced. Coupling is accomplished by using mineral oil, petroleum jelly, or water, but ultrasound coupling gel is most commonly used. Lubricants such as KY Jelly™ are disadvantageous since they contain air that decreases the energy being transferred to the patient. Energy loss because of inadequate coupling will cause reflection at the skin surface and can stimulate skin receptors and is painful; maximizing coupling reduces pain during treatment.<sup>15</sup>

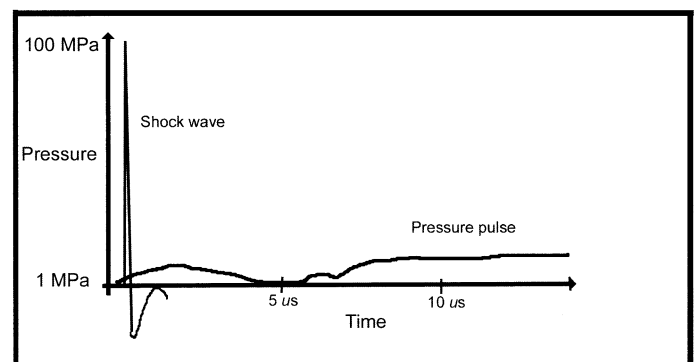
### Ballistic or Radial Waves

Ballistic radial pressure wave devices that are low cost generators have become available recently but are different from the previously described generators. As this name implies, the generated waves spread in a radial manner resulting in energy loss proportional to 1/radius.<sup>2</sup> As the distance between the source and target is doubled, only one fourth of the energy will hit the target. The maximum energy is highest at the source or, when coupled to tissue, on the skin surface and dissipates as distance increases.

The term ballistic or radial refers to how energy is generated. To produce ballistic waves, a projectile is accelerated to high speed by means of a precisely controlled burst of compressed air. When the projectile hits the probe installed in the hand piece, the impact energy is partially transformed into shock wave energy, which is, in turn, transmitted through the probe and coupled at the probe tip. Energy is transmitted in the probe as a result of the flexible deformation of the probe itself. Originally, ballistic waves were delivered via a semiflexible uretero-

scope to destroy ureteral stones. The hand piece has been modified to treat superficial structures in horses.

Pressure pulses from ballistic generators are substantially lower in amplitude and have longer rise time and pulse duration compared with a “true” focused shock wave (Fig 6). The air pressure-accelerated projectile has a speed of 2 m/s up to 20 m/s, which is 2 orders of magnitude lower than sound velocity in water or tissue. A “true shock wave” is produced when the projectile speed is comparable or higher than the speed of sound in tissue. Another difference exists between radial and true shock waves at the point of impact. When a radial wave impacts the tissue it is concussed uniformly; when focused shock waves impact the concussion undulates into the tissue. There is a different mechanical effect because the radial pressure wave generates huge pressure gradients between cells. For further information the reader is referred to an excellent over-



**Fig 6. The difference between a shock wave and a ballistic pressure wave is illustrated. Very little data about the physical properties of the ballistic waves are known. Generated pressures of 0.1 to 1 MPa and pulse durations of 1 to 5 ms are quoted. Compared with the true shock wave generators, maximum pressures are 100 times lower and pulse durations are 1,000 times longer.**

view at <http://www.storzmedical.com/English/Technology/Shockwaves.html>. The clinical relevance of the differences between radial and focused shock waves is unknown.

A comparison between an electrohydraulic shock wave generator and the ballistic wave generator was completed.<sup>16</sup> The wave from the ballistic generator was not focused but a  $-6$  dB zone was identified being 15 mm long and 10 mm wide. Shock waves produced by the electrohydraulic generator produced measurable cavitation with a lifetime that increased from 110 to 140  $\mu$ s, whereas it was not possible to detect cavitation at all from the ballistic generator. In that study, these 2 devices had markedly different physical characteristics. Because acoustics and cavitation are the principle mechanical mechanisms that govern shock wave actions, these 2 devices, namely radial and focus shock wave generator, cannot be considered equal. These devices may have entirely different clinical effects. A head has been developed to focus the ballistic wave. The depth-dependent pressure plot shows the highest pressure at the tip of the therapy head and a smaller peak at a depth of approximately 20 mm.

### Mechanisms of Action

According to laws of physics shock waves should be predictable, but when used in biologic systems, predicting the effect of shock wave therapy is challenging. Different shock waves can induce different outcomes. Variation in time to maximal pressure can change the effect of shock wave on cells.<sup>17</sup> Changes in energy density can alter the cellular effect, ranging from the development of intercellular gaps to frank detachment of endothelial cells and basement membrane damage.<sup>18,19</sup> Shock waves applied at a rate of  $\geq 15$  shocks/s created more damage to kidneys as a result of cavitation, when compared with shock waves applied of a slower rate.<sup>20</sup> Shock waves with a strong tensile portion decreased cell numbers in vitro by 99.9%.<sup>21</sup> It may be possible to modify the generator to maximize the desired effects but to minimize the negative effects.<sup>10</sup> Additional work is needed to correlate the desired outcome with the physical properties of the shock wave.

Another consideration is that shock waves studied in vitro may be different from the waves studied in vivo. Shock waves have a larger focal volume in vivo than in vitro, likely because of tissue inhomogeneity.<sup>13</sup> Larger focal volume may explain why pleural hemorrhaging developed in dogs after shock wave therapy was focused on the gall bladder. Shock waves generate different responses in different tissues and time frames. For example, in dogs shock waves caused neovascularization of the Achilles–calcaneous bone–tendon interface but reduced blood flow in neoplastic tissue. The effects of energy, frequency, and different waveforms are not yet fully understood.

### Cellular

The mechanism of action of shock waves was initially studied using cell cultures. The results of these studies, while interesting, may not be applicable to whole tissues. Cytotoxicity of shock waves can change based on the type of culture dish and the presence or absence of acoustic interfaces.<sup>22</sup> Cells in suspension are more susceptible to cytotoxic effects than those in pellet form or those embedded in gel.<sup>23</sup> Cell types differ in susceptibility to high energy shock waves.<sup>23,24</sup>

The cell membrane can be altered by shock waves of 0.12

mJ/mm<sup>2</sup> and is the most sensitive part of the cell.<sup>19</sup> A transient yet nonfatal increase in cell membrane permeability occurs.<sup>25</sup> During shock wave therapy, molecules up to 2 million daltons in size can enter the cytoplasm because of changes in cell permeability.<sup>26</sup> Macromolecules such as fluorescein dyes can be driven into the cell cytoplasm during shock wave therapy.<sup>27</sup> This effect may allow for photodynamic tumor treatment and gene therapy. Experimentally, oligonucleotides have been successfully delivered into the cell cytoplasm.<sup>28</sup> Ribosome-inactivating proteins were successfully delivered to tumor cells and, in doing so, reduced the concentration of a drug used to alter cell proliferation by up to 40,000 times.<sup>29</sup> In vivo studies in mice showed that after shock wave therapy fibrosarcoma growth was reduced and long-term remission was possible.<sup>29</sup> Since shock waves alter cell membranes it may be possible to combine treatment with chemotherapy. When a drug was present during shock wave treatment there was an enhanced effect.<sup>30</sup> In vivo shock wave therapy appears to have less direct effect on cells and more direct effect on tumor microcirculation. Vessel walls were destroyed and there was a notable temporary decrease in tumor perfusion.<sup>31,32</sup> When the environment was favorable for cavitation bubbles, tumors were completely removed in laboratory studies.<sup>33</sup> Shock wave generators with desirable shock waves may allow for more specific treatment protocols. To date, clinical application of shock waves for the management of tumors has been approached cautiously. There is potential for inducing metastasis by physically loosening cells.

### Bone

Potential mechanisms of shock wave activation of bone have been investigated in vitro. Shock waves can promote bone marrow stromal cell growth and differentiation into osteogenic cells.<sup>34</sup> Shock waves enhanced growth of bone marrow stromal cells and the production of TGF- $\beta$ 1. Further investigations showed that this response may be the result of the effects of shock waves on cell membranes.<sup>35</sup> Induction of osteogenic transcription factor and type 1 collagen mRNA expression showed that shock waves can transduce a biologic response from membrane potential changes. These data show that there is likely a direct effect of shock waves on bone formation that warrants further in vivo investigation.

Free radical production could explain some of the effects of shock waves and bone formation. Superoxide production was followed by increased concentrations of TGF- $\beta$ 1.<sup>36</sup> Shock waves generated free radicals<sup>37,38</sup> and increased the intracellular concentration of an indicator dye for free radicals.<sup>37</sup> The free radicals can be generated intra- or extracellularly. Nitric oxide, a free radical that acts as a secondary messenger in multiple biological pathways, may be important in fracture repair.<sup>39</sup>

In addition to free radicals other intercellular messages have been investigated. In a rabbit model the substance P concentration that can cause osteoblast proliferation was consistently higher in the periosteum of shock wave-treated femurs at 6 and 24 hours, and at 6 weeks.<sup>40</sup> Substance P may induce neurogenic inflammation that could lead to an irritation and activation of periosteum. However, since prostaglandin E<sub>2</sub> concentrations did not increase, it is unlikely that inflammation is the sole mechanism of action.

Interest in the application of shock wave therapy to various orthopedic injuries was initially stimulated by the finding that

after the modality was focused on the ureter, bone remodeling of the pelvis occurred.<sup>41</sup> The first in vivo study of high energy shock waves in rabbits resulted in periosteal elevation, dose-dependent osteonecrosis, and disruption of cancellous bone.<sup>42</sup> When evaluated over a 12-week period, bone formation occurred as seen radiographically and histologically. As early as 1991, dose-dependent osteogenesis was confirmed by using fluorescent microscopy.<sup>43</sup> Subsequently, it was shown that with high energy (1.2 mJ/mm<sup>2</sup>) shock wave therapy, there was significantly more bone formation in the proximal femur of rabbits, even outside of the treatment focal zone, when compared with low energy (0.9 mJ/mm<sup>2</sup>) shock wave therapy and placebo treatments.<sup>44</sup>

Shock wave therapy was used in a radius defect model in rabbits and similar results were found.<sup>45,46</sup> Treated bones had greater callus formation than untreated bones and, histologically, healing appeared to be less mature. Exuberant callus and induction of osteogenesis may be of more benefit in patients with nonunion than in those with acute fractures. Shock wave therapy may be useful in callus-lengthening procedures.

Shock wave therapy has shown promise when used in vivo in experimental nonunion models. Twelve weeks after radial osteotomy, an electromagnetic generator was used to administer 4,000 pulses at 0.54 mJ/mm<sup>2</sup>, distributed primarily at the ends of the bone in experimental dogs.<sup>47</sup> Control dogs were managed similarly, but did not receive shock wave therapy. One of 5 treated dogs and 4 of 5 control dogs had persistent nonunions.<sup>47</sup> In another study 8 mixed-breed dogs underwent tibial osteotomy (3 mm fracture gap) and bone plate application bilaterally.<sup>48</sup> Immediately after surgery, shock wave therapy using 2,000 pulses at 0.18 mJ/mm<sup>2</sup> from an electrohydraulic generator was performed. At 12 weeks, treated legs had significantly greater callus and cortical bone formation, and bone was thicker and denser.

In a promising early study of people with nonunions 85% of the fractures healed (82 patients) using shock wave therapy.<sup>49</sup> More recently Schaden achieved 76% osseous union rate in 115 people with nonunions.<sup>50</sup> Case selection may improve success rate. Patients with fracture gaps > 5 mm and unstable fractures are not candidates for shock wave therapy. People with avascular or hypoplastic nonunions respond poorly to treatment.<sup>51</sup> People with nonunions of 6 months or more duration were less painful, had greater weightbearing, more callus, and a decreased fracture gap by 3 months after shock wave treatment compared with their condition before therapy.<sup>51</sup> Seventy-two percent of patients with nonunions of the tibia or femur of 9 months' duration had osseous union in a mean of 4 months.<sup>52</sup> Heavy smoking was identified as a negative factor for a successful outcome. Additional therapy in patients that did not respond to the initial treatment was found to improve success. Shock waves can be used with orthopedic implants in place. Therapy must be directed at the treatment site around the hardware, but the mere presence of hardware will not adversely affect outcome.<sup>53</sup>

An area of current interest is the treatment of femoral head osteonecrosis in people. Previous treatments were aimed at delaying the need for total hip replacement rather than treating the primary disease and in only 23% of patients was this approach successful.<sup>54</sup> A study in 22 adults found that after shock wave therapy 14 of the 22 patients (66.7%) were improved.<sup>55</sup> Pain decreased initially and remained decreased and the Harris Hip Score, a combination of factors including ambulation and

mobility, improved in these patients. The results obtained so far suggest that high energy shock wave therapy may offer an alternative to invasive treatment modalities for femoral head osteonecrosis.

## Tendons and Ligaments

ESWT is routinely used for the treatment of insertional desmitis in people. Eighty-six percent of 468 patients with enthesopathy with at least 3 months' follow-up, primarily radial epicondylitis, had good a result.<sup>56</sup> Of 396 human athletes 296 had very good or good results compared with 20 with an unsatisfactory outcome.<sup>56</sup> Shock wave therapy has gained widespread use for many soft tissue injuries in people. The first FDA approval was for the use of an electrohydraulic generator for the treatment of plantar fasciitis. In a randomized double-blind evaluation more treated patients had a positive outcome by all 4 of the evaluation criteria than did those receiving placebo treatment.<sup>57</sup> Unfortunately, the disease processes seen in people are not well correlated with those seen in horses.

Potential complications of ESWT have been investigated in laboratory animals. To determine if shock waves can cause tendon damage in rabbits, Achilles tendons were treated with 1,000 pulses with incrementally increasing energy.<sup>58</sup> Dose-dependent inflammation was observed and it was determined that EFD over 0.28 mJ/mm<sup>2</sup> should not be used. While this rabbit model identified potential complications, higher energies are routinely used in other species without complications. People with calcification of the rotator cuff are usually treated with ESWT. The effect of ESWT on material properties of tendons was investigated in a model using mineralized gastrocnemius tendons in turkeys.<sup>59</sup> At EFD of 0.6 mJ/mm<sup>2</sup> there was no effect on tensile strength, but at 1.2 mJ/mm<sup>2</sup> tensile strength decreased.<sup>59</sup>

The effect of shock wave therapy (1,000 pulses at 0.18 mJ/mm<sup>2</sup>) on the Achilles tendon-bone junction in dogs was evaluated.<sup>60</sup> Microscopically, new capillaries and muscularized vessels and myofibroblasts were found in treated specimens. Myofibroblasts and neovascularization were not found in untreated specimens. Neovascularization may be an important component of healing and may potentially explain decreased pain following ESWT for insertional desmopathy.

## Dose Dependence

The effects of shock waves are dose dependent. There appears to be no effect at low energy/low pulse, a desired effect at midrange levels and a destructive effect at high energy and high pulse numbers. When shock waves were evaluated in partial-thickness wounds in pigs, low energy treatment enhanced healing and the tissue had a larger number of microvessels.<sup>61</sup> Healing was impeded at higher energy and pulse numbers. Similarly, in formalinized rabbit bone shock waves were capable of creating anything from microfractures to gross cortical defect.<sup>62</sup> In vitro, the proliferation of human chondrocytes and ovine bone marrow stromal cells (BMSCs) were evaluated at EFDs of 0, 0.02, and 0.06 mJ/mm<sup>2</sup> and 0, 500, and 1,000 pulses.<sup>63</sup> BMSCs showed a dose- and pulse-dependent proliferative response although the results were not significant. Chondrocytes had less proliferative potential than untreated controls and were not positively affected. Shock wave therapy may have different effects on osteocytes and chondrocytes, a concept that



should be kept in mind when managing diseases such as femoral head osteonecrosis.

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