Shock Waves (1994) 4:55–72

Shock Waves

Medical applications and bioeffects of extracorporeal shock waves

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Recieved October 4, 1993; accepted May 25, 1994

Abstract. Lithotripter shock waves are pressure pulses of microsecond duration with peak pressures of 35–120 MPa followed by a tensile wave. They are an established treatment modality for kidney and gallstone disease. Further applications are pancreatic and salivary stones, as well as delayed fracture healing. The latter are either on their way to become established treatments or are currently under investigation. Shock waves generate tissue damage as a side effect which has been extensively investigated in the kidney, the liver, and the gallbladder. The primary adverse effects are local destruction of blood vessels, bleedings, and formation of blood clots in vessels. Investigations on the mechanism of shock wave action revealed that lithotripters generate cavitation both in vitro and in vivo. An increase in tissue damage at higher pulse administration rates, and also at shock wave application with concomitant gas bubble injection suggested that cavitation is a major mechanism of tissue damage. Disturbances of the heart rhythm and excitation of nerves are further biological effects of shock waves; both are probably also mediated by cavitation. On the cellular level, shock waves induce damage to cell organelles; its extent is related to their energy density. They also cause a transient increase in membrane permeability which does not lead to cell death. Administered either alone or in combination with drugs, shock waves have been shown to delay the growth of small animal tumors and even induce tumor remissions. While the role of cavitation in biological effects is widely accepted, the mechanism of stone fragmentation by shock waves is still controversial. Cavitation is detected around the stone and hyperbaric pressure suppresses fragmentation; yet major cracks are formed early before cavitation bubble collapse is observed. The latter has been regarded as evidence for a direct shock wave effect.

Key words: Bioeffect, Cavitation, ESWL

1. Introduction

Extracorporeal shock waves are single pressure pulses of microsecond duration with peak pressures of 35–120 MPa which are employed for the treatment of kidney and gallstones. They are produced by the focusing of pulses which are generated in water outside the body. The latter are coupled on a relatively large area through the skin, propagated in tissue and focused on the kidney or gallstone by means of an ultrasound or X-ray localizing device (Fig. 1). During patient treatment, shock waves are administered slowly and often synchronous with the heartbeat. Extracorporeal shock waves generally contain a tensile wave which is caused by diffraction effects during focusing.

Interest in the bioeffects of shock waves arose in 1971 when it was first demonstrated that shock waves could destroy kidney stones (Häusler and Kiefer 1971). The authors generated a shock wave in a water basin by a high speed water drop, and focused it on the stone. Following a number of in-vitro and animal studies which established their fragmentation effectiveness and comparably minor tissue effects (Chaussy 1982), extracorporeal shock waves were first applied in 1980 to destroy kidney stones in patients (Chaussy et al. 1980). Kidney stone fragmentation is still the most important medical application of shock waves. Gallstone fragmentation and other indications have followed or are currently under clinical or laboratory investigation. Side effects of clinical shock wave application and the prospect to widen the range of applications triggered a growing number of animal experiments on the bioeffects of shock waves. Therefore, during the last years, knowledge about these effects and the mechanisms of action has increased.

In the next chapter, the physical parameters of extracorporeal shock waves and the methods of their generation will be briefly mentioned, followed by a survey of todays' spectrum of medical shock wave applications. Subsequently, the generation of cavitation by lithotripters will be introduced because it is an important mediator of biological shock wave effects, to focus afterwards upon the bioeffects at several organs and single cells. Covering the bioeffects in depth would be far beyond the scope of this review; emphasis will instead be placed on the principal effects and mecha-

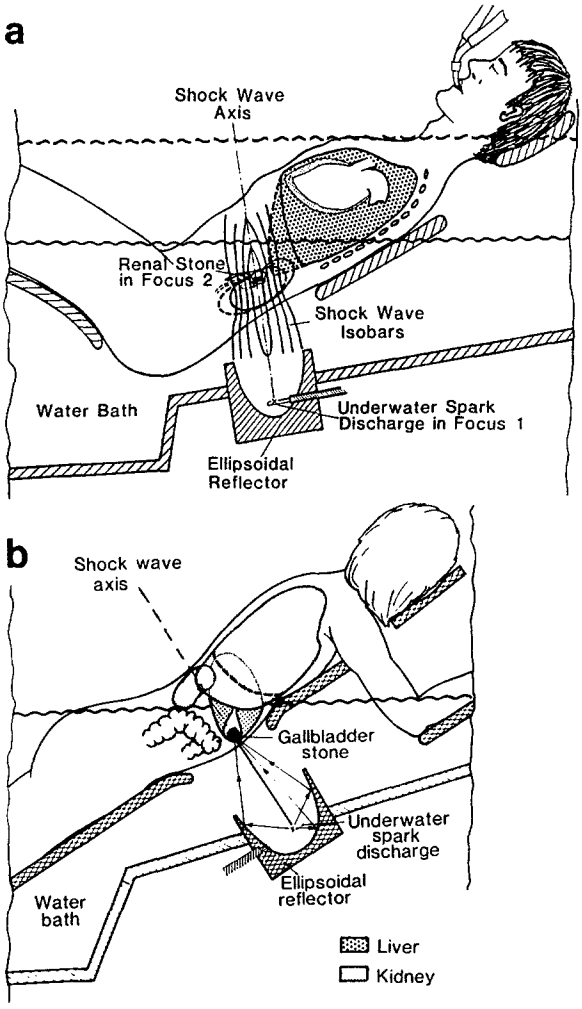

Fig. 1a, b. Positioning of patient and shock wave source during lithotripsy. **a** Patient lying on his back for kidney stone fragmentation. Shock waves are focused to the renal pelvis, potential shock wave damage is restricted to the region of the isobars. **b** Patient in prone position for gallstone fragmentation. Shock waves are focused to the gallbladder. The figures depict patient positioning in a bathtub lithotripter; it is similar in more modern lithotripters with a water bag coupling of the shock wave source to the body (from Weber et al. 1987 and 1989)

nisms. Fragmentation effects and mechanisms will be spared till the end. Another review of the physics and bioeffects of extracorporeal shock waves has recently been published (Coleman and Saunders 1993).

2. Lithotripter shock waves

2.1. Physical parameters

Shock waves from lithotripters are considered weak in the gas dynamic sense, and nonlinear effects become only apparent in proximity to the focus (Mueller 1987). In the focus, the lithotripter pulse is composed of a positive half-cycle of 1–3 μs (Fig. 2) with dominant pulse frequencies of 200 kHz–1 MHz (Coleman and Saunders 1987a; 1989; 1993). Depending on the lithotripter type and power setting, its peak pressure varies between 35 and 120 MPa. At high output settings, the risetime of the shock front is generally below 30 ns. It has not been exactly determined since it is not correctly picked up by the commonly employed polyvinylidenedifluoride (PVDF) hydrophones. The positive half- cycle is followed by a diffraction-induced tensile wave which is registered by PVDF hydrophones as a 5–10 MPa pulse of a few μs duration. These values are probably too low because the low adhesion between PVDF and water leads to an early loss of contact between foil and fluid. Using a fiber optic probe hydrophone which takes advantage of the higher adhesion of silica and water, tensile waves up to 15 MPa have been detected in lithotripters (Staudenraus and Eisenmenger 1993). More details on the physical properties of lithotripter shock waves are published elsewhere (Coleman and Saunders 1993). The focal size is commonly used to describe the spatial pressure distribution of the acoustic field of a lithotripter. It is defined as the region where at least half-maximal peak pressures are obtained. Since it depends solely on the peak pressure in the focus and omits other parameters of the pressure profile, its usefulness is questionable. According to this term, lithotripters with high peak pressures have automatically smaller focal sizes due to the higher half-maximal pressures.

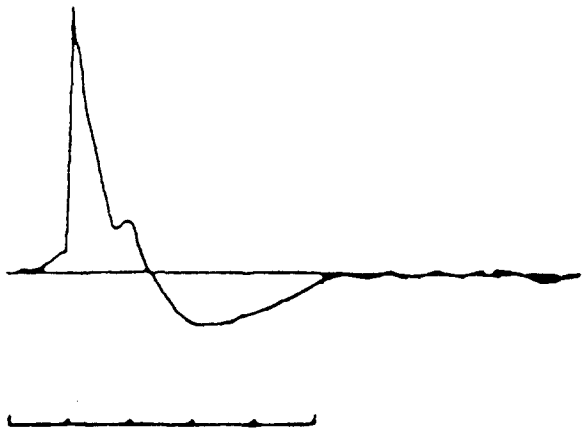

Fig. 2. Typical temporal pressure profile of a lithotripter pulse in the focus of an electrohydraulic lithotripter. A positive pressure pulse is followed by a tensile wave (from Coleman et al. 1987a)

Peak energy density and pulse energy are determined from the temporal and spatial distribution of the pressure profile. Peak energy densities of lithotripters are commonly in the range of 0.1–1 mJmm^{-2}, and pulse energies in the range of 10–100 mJ (Folberth et al. 1992, Dornier lithotripters technical data sheets). The importance of the pulse energy for the characterization of a lithotripter field is now increasingly recognized.

2.2. Shock wave generation

Shock waves are generated in lithotripters according to the electrohydraulic, electromagnetic, and piezoelectric principle. Electrohydraulic shock waves are generated by underwater spark discharge between the tips of an electrode (Fig. 3a). The electrode is localized in the focus of an ellipsoidal reflector which bundles the spherically diverging pulse into its second focus. Explosive pellets have been used

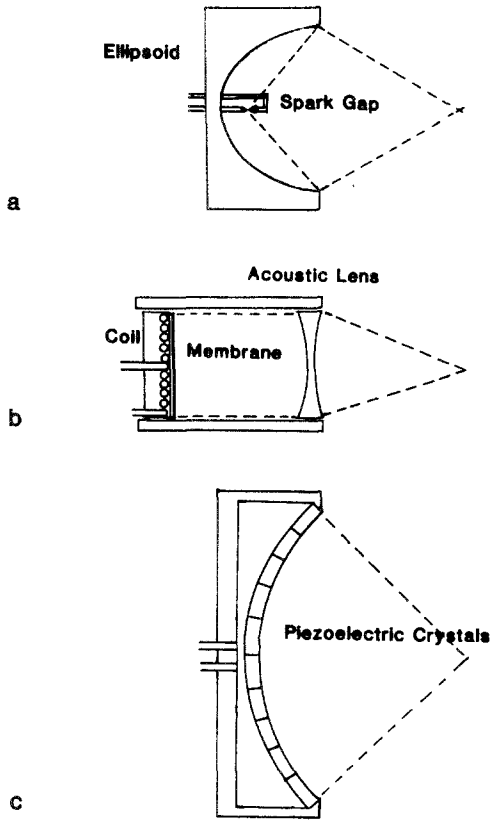

Fig. 3a–c. Principles of shock wave generation in lithotripters: **a** electrohydraulic, **b** electromagnetic, and **c** piezoelectric shock wave generation. For explanation see text.

instead of the electrode (Kuwahara et al. 1986); electrode replacement by a focused laser beam was not found to be an advantage.

Electromagnetic shock waves are generated by a metal membrane overlying a flat coil at one end of a water-filled tube, a design originally described by Eisenmenger (1964) (Fig. 3b). A high current in the coil repels the membrane and generates a plane wave which is focused by an acoustic lens. An alternative design has been developed, in which a cylindrically diverging wave is generated by an electromagnetically driven cylindrical membrane. It is focused by a paraboloid reflector, and does not have to pass through an acoustic lens (Köhrmann et al. 1992).

Piezoelectric shock waves are generated by 30–3000 piezoceramic crystals mounted on the inner surface of a spherical dish (Fig. 3c). Upon stimulation by electric discharge, they emit a pressure pulse which is, without additional means, focused to the center of the sphere. The rear side of the dish has an irregular contour to prevent the formation of a strong tensile wave.

All shock wave sources are powered by 40–1500 nF capacitors charged with 2–30 kV. The exact requirements for the electric circuits depend on the type of the source and are described elsewhere (Coleman and Saunders 1993). The type of the source determines also the shape of the pulse. From their point of generation onward, pulses from electrohydraulic sources show a steep rise of the shock front all along their path of propagation. Using a combination of optical shock front detection and hydrophone pickup, the risetime of a spherically diverging shock from optical breakdown was found to be less than 10 ns (Vogel et al. 1989); the risetime of a plane 10 MPa shock front is known to stabilize in water at about 1 ns (Eisenmenger 1964). Values in a similar range should be expected in electrohydraulic lithotripters. Pulses from electromagnetic and piezoelectric sources have obviously longer risetimes at their points of generation (Coleman and Saunders 1989). During propagation in water, they steepen increasingly due to nonlinear acoustic effects. This is most pronounced at high output settings where risetimes below 30 ns are reached in the focus.

The focal angle, i.e. the angle under which the outer rays of the focused wave meet in the focus, is an important determinant of the focal peak pressure (Mueller 1987; 1988). A wide focal angle leads to a high pressure; nonlinear effects are only prominent at a distance of a few millimeters in the focal area. A small focal angle, on the other hand, leads to a low focal pressure; nonlinear effects are prominent over a long distance during shock propagation. This is associated with a deviation of the acoustic from the geometric focus. Todays piezoelectric sources have always wide angles since the relatively low acoustic energy emitted per crystal area forces engineers to use large generator areas to achieve adequate output. As a consequence, these devices generally generate high peak pressures. Electrohydraulic and electromagnetic sources are available with both wide and small focal angles, thus covering a wide range of peak pressures.

The pulse shape can be varied in electromagnetic and piezoelectric pulse generators but principally not in electrohydraulic generators. This feature might become important in the future if certain waveforms prove to be of advantage in lithotripsy. The topic has however not yet been examined.

3. Medical applications

3.1. Kidney stone fragmentation

Around 3 % of the male English population have a urinary stone at some point during their life, females are only half as often affected (Robertson et al. 1983); figures are 6 % and 4 % for West Germany (Vahlensieck et al. 1980), and 5 % for Japan (Yoshida and Okada 1990). Only part of the stone-bearers require treatment since a high percentage of stones are passed spontaneously. Nevertheless in 1979, 40 000 operations were performed for urinary stones in Germany (Eisenberger and Miller 1987). The mortality of open surgery for a kidney stone has been quoted to be 0.8 % (Wickham 1990).

Nowadays, extracorporeal shock wave lithotripsy is the method of choice for the treatment of more than 80 % of stones in the kidney and ureter; it has already been applied in millions of patients. Stones up to 20 mm in size are ideal candidates, they are treated by shock waves only (Lingeman et al. 1986). Larger stones and multiple stones are treated at most centers by a combined approach: a probe (mechanical, laser, or ultrasound) is introduced via the skin to the pelvis of the kidney, the stone is fragmented by direct contact, and the fragments are pulled out. Usually only part of the stone mass can be removed this way, and the rest is fragmented

by extracorporeal shock waves (Lam et al. 1992). In some places, even large stones are treated by shock waves only (Constantinides et al. 1989; Miller et al. 1990). Open surgery has been nearly completely replaced by these approaches, it is nowadays indicated in only 1 % of stone treatments.

During a treatment session, 1000–4000 discharges are applied; their exact number depends on the stone and the type of lithotripter. The weaker piezoelectric machines require higher pulse numbers (Bierkens et al. 1992). Shock wave application by the stronger electrohydraulic and electromagnetic lithotripters is usually coupled to the patient's electrocardiogram, and a single pulse is administered during the cardiac refractory period. There was a general trend over the past years to apply a higher number of discharges with lowerpulse energy, independent of the type of the employed lithotripter. In the case of incomplete fragmentation, which is assumed when fragments larger than 5 mm are encountered on a control X-ray, retreatment is performed. Retreatment rates vary between 5 % and 50 %, being again higher for weaker lithotripters. The stone fragments are passed with the urine, and around 70 % of patients are stone free 3 months after treatment (Drach et al. 1986; Lingeman et al. 1986). The location of the fragments determines their clearance; fragments in the lower kidney pole remain more often in place since they have obviously difficulties to leave their dependent position to reach the ureter against gravity.

The advantages of extracorporeal shock wave lithotripsy over surgery are obvious. Treatments are performed without general anaesthesia. Intravenous administration of pain killing drugs is sufficient, and many treatments with piezoelectric lithotripters are performed without any medication. Furthermore, patients can be treated as outpatients without hospitalization. The major advantage, however, is a dramatic drop of the mortality of stone therapy to virtually nil which has already saved the lives of thousands of patients (Whickham 1990).

Extracorporeal shock wave lithotripsy has, however, also side effects which consist of bleedings in the kidney and obstruction of the urine flow by stone fragments. Blood-stained urine is an almost universal finding during treatment. It indicates tissue damage to the organ but is usually of no practical significance. Tissue changes in or around the kidney, supposed to consist of swelling, fluid accumulation, and bleeding, can be picked up in up to 90 % of patients by sensitive imaging methods (Kaude et al. 1985; Grote et al. 1986), yet there are usually no clinical symptoms. Renal subcapsular bleedings and bleedings into the surrounding tissue which were large enough to be detected by ultrasound have been found in 0.7 % of treatments (Knapp et al. 1988). Therapy consisted of blood transfusions while surgery was not indicated. Large bleedings requiring removal of the kidney have been reported, as has death from severe bleeding (Stoller et al. 1989). In 10 % of patients, stone fragments obstruct the ureter and block urine flow; retreatment or their mechanical removal is indicated when no spontaneous passage occurs.

3.2. Gallstone fragmentation

Population studies indicate that stones are found in the gallbladder of about 10 % of the general population of England and Italy, thus exceeding the prevalence of kidney stones (Roda et al. 1989). Like kidney stones, more than 80 % of gallstones stay asymptomatic, the remaining patients require treatment which, from the end of the last century on, consists of surgical removal of the gallbladder. The operative mortality of this simple procedure is less than 0.2 %. It has not been established that conservation of the gallbladder is of any physiological advantage. This is a major difference to the kidney where organ preservation is of vital importance.

Extracorporeal shock wave lithotripsy of gallbladder stones (reviewed by Barkun and Ponchon 1990) has been first applied in 1985 (Sauerbruch et al. 1986). Up to now, an estimated 100 000 patients have been treated. From the beginning, the indication has been restricted to patients with up to 3 stones in their gallbladders, and a stone volume not larger than 5–7 cm^3. The reason for these limitations is the limited destruction efficiency of todays lithotripters. Other prerequisites for lithotripsy are a good gallbladder emptying and a patent cystic duct to allow the passage of fragments. According to these criteria, only 15–20 % of referred patients have been found to be candidates for gallstone lithotripsy (Sackmann et al. 1988).

During shock wave treatment, the stones are localized by ultrasound and 1000–4000 discharges are applied. Treatment is only considered successful if the gallbladder is stone free. Most centers prescribe bile acids as an oral medication after lithotripsy in order to dissolve fragments in the gallbladder. Widely varying success and retreatment rates have been reported, which is probably due to different degrees of fragmentation and fragment sizes. Good fragmentation results were achieved by discharges of high pulse energy, and 80 % of gallbladders with stones up to 20 mm size were stone free 9–12 months after treatment (Sackmann et al. 1988; 1991). In the same study, using a lower pulse energy at a similar number of discharges, this rate was reduced to 60 %; other groups reported even lower success rates. There is evidence that the clearance of fragments from the gallbladder is faster when fragments are smaller than 3 mm (Sackmann et al. 1991) or even pulverized (Soehendra et al. 1994).

More recently, attempts have been made to treat patients with higher numbers of gallstones and larger stone volumes. This required a higher number of discharges and multiple treatment sessions. Using up to 36 000 discharges, a stone free rate of 60 % was achieved after 12 months (Darzi et al. 1991). According to conventional entry criteria, over two thirds of the patients of this study would have been excluded from treatment. In another study, 80 % stone freedom was achieved after 12 months (Soehendra et al. 1994). Up to 26 000 discharges had to be administered in 1–20 (median 3) treatment sessions in order to achieve complete pulverization of the gallstones. Most remarkably, 80 % of the referred patients were included in this study, and no bile acids were administered to dissolve the fragments. So there are ways to treat most gallstone patients by extracorporeal shock waves, but they are time consuming and need to be improved.

Side effects of gallstone fragmentation are nearly exclusively due to the passage of fragments from the gallbladder via the bile ducts into the gut. They consist of attacks of abdominal pain caused by fragments obstructing the bile ducts, of jaundice because the fragments can also block the outflow of bile from the liver, and of inflammation of the pancreas because they can block the outflow of pancreatic juice. Preventable death has been reported as a consequence of pancreatic inflammation because an obstructing fragment had not been removed (Vellar et al. 1993). Shock wave induced bleeding into the liver and the gallbladder bed (McGrath et al. 1990) and even perforation of the gallbladder (Janowitz et al. 1992) have been observed but seem to be quite rare.

Since the gallbladder is left in place, new gallstones can be formed after lithotripsy. This happens in 20 % of the patients within the following 5 years (Sackmann et al. 1992), and is a major argument against gallbladder conservation. The main reason for the as yet limited success of shock wave lithotripsy for gallstones is, however, a dramatic change of the surgical technique of gallbladder removal during the last years. It is now done under endoscopic view by manipulation in the closed abdomen (laparoscopic cholecystectomy). Surgical instruments are introduced via finger-thick working channels, and the gallbladder is finally pulled out through one of these channels. Compared to the open operation, hospitalization has been shortened to one or two days, and pain is reduced. This diminished the previously considerable advantages of lithotripsy. If lithotripsy of gallbladder stones is to be successful, the procedure must become as easy as going to a dentist where repeated short visits are generally accepted.

Another, less common indication for shock wave treatment is the fragmentation of large stones obstructing the common bile duct. It is only indicated after attempts have failed to remove the stones endoscopically by placing a basket around them to pull them out. Lithotripsy is a real problem solver in this situation (Sauerbruch and Stern 1989). All over, an estimated several thousand treatments have been performed for this condition. Since endoscopic access is required, there are alternatives to extracorporeal shock waves like laser lithotripsy which make use of the direct access to the stone.

3.3. Pancreatic stone fragmentation

The treatment of kidney and gallstones by shock waves triggered attempts to fragment also stones at other locations in the body. Stones in the pancreatic duct are generated during chronic pancreatic inflammation. Extracorporeal shock wave lithotripsy with subsequent endoscopic removal of the fragments has been first applied in 1986 (Sauerbruch et al. 1987); several hundred patients have been treated so far. In the largest reported series, half of them experienced pain relief, and pancreatic function improved in a subset (Delhaye et al. 1992). Shock wave lithotripsy of pancreatic stones is evolving as a safe and effective alternative to surgery.

3.4. Salivary stone fragmentation

Salivary gland stones are said to affect 12 out of 1000 people (Iro et al. 1992). The first report of extracorporeal shock wave application to a salivary stone appeared in 1989 (Iro et al. 1989). A piezoelectric lithotripter was applied which makes less noise than the other types, an important feature when shock waves are released in proximity to the ear. Later, experience has also been gained with an electromagnetic lithotripter (Kater et al. 1992). It is estimated that several hundred patients have been treated so far. The method can be performed on an outpatient basis and might in the future replace surgery in many cases.

3.5. Fracture healing

Beyond stone fragmentation, extracorporeal shock waves are at present an experimental treatment for non-healing fractures. The first reports about treatments of patients with delayed union or non-union of fractures appeared in 1991 (Valchanou and Michailow 1991). Application of 1000–4000 shock waves of high pulse energy was said to induce bony union in 85 %. An effect of similar or somewhat lower magnitude has also been reported by another group (Schleberger and Senge 1992). This new application seems promising. Up to the present, however, only few treatments have been performed. A European multicenter trial is currently under way to evaluate the clinical success; its results have to be awaited before the merits of the method can be judged.

4. Cavitation in lithotripters

Lithotripters generate cavitation, which is defined here as the movement of newly formed and preexisting bubbles containing gas or vapor in a fluid (reviewed by Apfel 1981; Crum 1982a). Cavitation is well known as a powerful mechanism of material damage from the beginning of this century when it was discovered that it causes surface erosion and failure of ship propellers, and of many other materials in which fluid moves fast along a solid boundary. Cavitation damage consists of surface craters caused by bubble collapse with concomitant water jet formation (reviewed by Steinberg 1993). Cavitation damage from a lithotripter is easily demonstrated by the generation of craters at the exposure of an aluminum foil in its water bath (Coleman et al. 1987b).

While evidence is strong for the role of cavitation in the generation of tissue damage, thermal effects of shock waves can be excluded since the discharges are administered at a low frequency of only 1–2 Hz. The temporal average acoustic energy is too low to cause significant tissue heating. Theoretical considerations point to an only minor temperature increase of 2 K even when discharges are administered at a rate of 100 per second (Filipczynsky and Piechocki 1990).

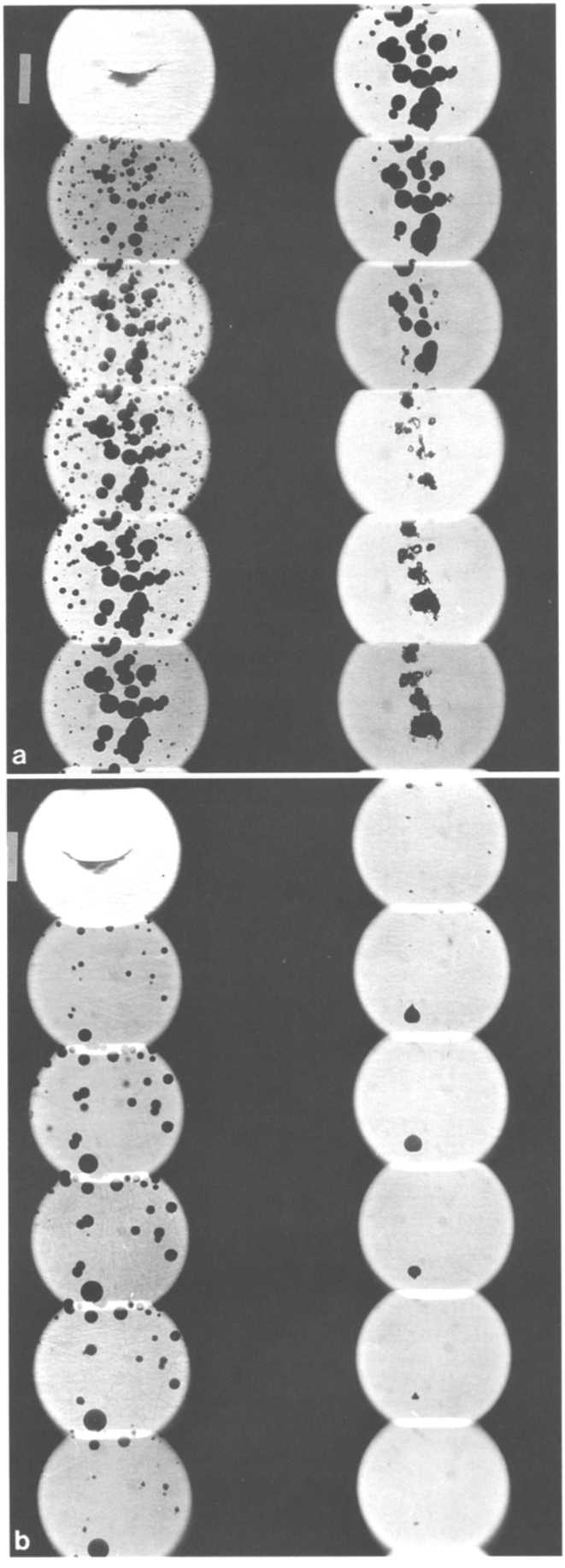

Fig. 4a, b. Cavitation along the central ellipsoidal axis in the water bath of an electrohydraulic lithotripter (Dornier XL1) photographed at a framing rate of 10 000 images/second. The bar denotes 10 mm. **a** At high gas saturation (O_2 content 6.0 mgL^{-1}), numerous bubbles are visible with a maximal diameter of 6 mm. Maximal bubble diameters are reached after 500–700 μs, the field has first collapsed after 900 μs. The second oscillation takes 500 μs. **b** At low gas saturation (O_2 content 0.8 mgL^{-1}), fewer bubbles are visible with a maximal diameter of again 6 mm. The maximal bubble diameter is reached after 400–500 μs, the field has first collapsed after 700 μs. The second oscillation takes 500 μs (K. Jungnickel, M. Delius, and A. Vogel, unpublished)

Two types of cavitation have been observed in lithotripters: the tensile wave generates cavities de novo, and the pressure pulse compresses preexisting gas bubbles.

4.1. Cavitation by tensile waves

The tensile wave expands invisible cavitation nuclei to visible, oscillating bubbles. Cavitation nuclei have not been directly visualized, their existence is strongly suggested by the fact that water cavitates under normal conditions at tensions below 1 MPa, two orders of magnitude lower than expected from theoretical considerations on its tensile strength (Apfel 1981). Nuclei are thought to consist of impurities, either minute gas bubbles stabilized by a lipid film (Yount 1984) or gas pouches in crevices at the surface of solid particles (Crum 1979; 1982b). It is in accordance with these assumptions that repeated filtering increased the tensile strength of water considerably (Greenspan and Tschiegg 1967).

Cavitation can be easily visualized in the water of a lithotripter tub. It occurs along the central axis of the shock wave field in an area of 10–20 mm diameter. When studied in the water bath of an electrohydraulic lithotripter, the bubbles reached maximal diameters of 5–7 mm after 500 μs (Fig. 4), and a second bubble oscillation followed during the next millisecond (Jungnickel unpublished). At a hard surface, lots of small cavities coalesced to a larger cavity which collapsed only after more than a millisecond, starting as expected at the contact site in the periphery where the bubble angle was smallest (Fig. 5).

As long as the surface of a bubble is large during the expansion phase, and its internal pressure is low, gas diffuses into its interior (Crum 1984). The duration of the subsequent collapse is shorter, and less gas diffuses out via the now smaller surface. As a net effect, gas is entrapped. According to a calculation of the gas exchange, bubbles up to 40 μm radius are finally generated by a 100 MPa lithotripter pulse (Church 1989). Observation of the focal area in the water bath of our electrohydraulic lithotripter revealed indeed many gas bubbles with diameters up to 40 μm at 1 second after passage of a shock wave (Fig. 6). Bubbles of 4 μm diameter have also been indirectly detected by a resonant bubble detector (Williams et al. 1989).

Lithotripters generate cavitation not only in the water bath but also in vivo where bubble formation has been visualized by diagnostic ultrasound. Two features have been differentiated: moving bubbles in veins which were flushed away with the blood flow, and tissue areas along the shock

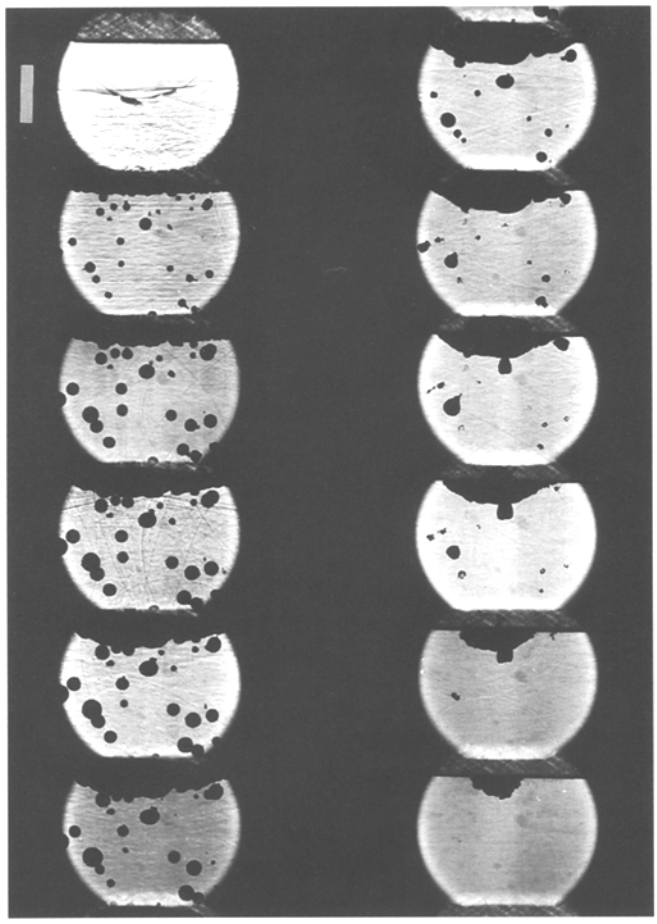

Fig. 5. Cavitation at a Plexiglas surface (upper part of each image) positioned in the focus of the lithotripter (framing rate of 10 000 images/second, bar = 10 mm). Small bubbles at the surface coalesce to a large bubble whose collapse takes place 1.5 ms after shock wave passage. The bubble collapses from the sides along the Plexiglas surface, and its center finally detaches from the surface (same source as Fig. 4)

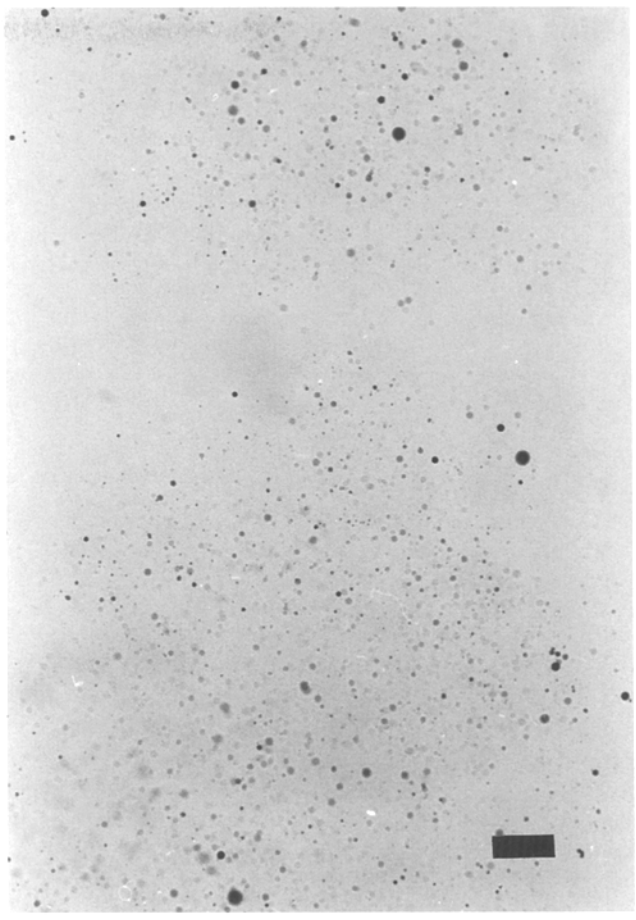

Fig. 6. Gas bubbles in the water of the lithotripter tub 1 second after shock wave release. Many small bubbles have been generated with diameters up to 40 μs. Before shock wave release, no bubble has been visible at all. The bar denotes 1 mm (same source as Fig. 4)

wave axis which were transiently brightened (Kuwahara et al. 1989; Delius et al. 1990a). One second after a pulse, the changes have largely disappeared. It is assumed that the ultrasound picked up the small visible gas bubbles which remained after the fast bubble oscillation. Since bubble diameters cannot be determined by diagnostic ultrasound, their size in vivo is not known. The occurrence of cavitation was associated with signs of damage to liver cells (Forer et al. 1992), and tissue damage was observed exactly at the sites where ultrasound signals were picked up (Delius and Gambihler 1992).

4.2. Shock wave-gas bubble interaction

Shock wave-gas bubble interaction is driven by the positive pressure pulse which collapses the wall of a preformed, stationary gas bubble asymmetrically (Dear and Field 1988). At the point of impact a water jet originates which moves in direction of the pulse. It has been shown that shock wave-gas bubble interaction generates faster jets and is more damaging than the collapse of a cavitation bubble which is driven by the ambient pressure in the fluid (Tomita and Shima 1986).

The interaction of a lithotripter shock wave with air bubbles positioned below a plastic foil has been investigated by high speed photography (Philipp et al. 1993). For bubble diameters of 0.15–1.2 mm, collapse times ranged from 1–9 μs; the results agreed well with the Gilmore model. Maximal water jet velocities of 400–800 m/s were obtained at bubble radii of 500–600 μm. The collapse of larger bubbles was slowed down by the tensile wave which followed the pressure pulse.

5. Bioeffects of shock waves

5.1. Effects on tissues

Extracorporeal shock waves have to pass tissue before they reach their target, and on their way they can cause damage. It is restricted to the high pressure area along the central axis of the shock wave field. The predominant lesion is generally damage of blood vessels which leads to bleedings; it is observed in all organs which have so far been exposed. Bleedings have typically a focal distribution with multiple bleeding spots; they do not affect all tissue within the damaged region in toto. Another feat ure occurring in association with damage of blood vessels is blood clots. Parenchymal

cells of an organ, e.g. liver cells in the liver and cells of filtration units in the kidney, are also affected, be it directly by the shock wave action or indirectly as a consequence of a decreased blood supply by clot formation.

In the following, the effects of shock waves at individual organ systems are briefly summarized. Only little information has been gained from human studies since patients are not operated on, and nearly all findings stem from animal experiments. Special emphasis is placed on those which gave hints to the mechanism of shock wave action. While many observations pointed to the involvement of cavitation, no evidence has so far been obtained in support of a direct, non cavitation-mediated shock wave effect. This does not mean, of course, that it does not exist.

5.1.1. Shock wave action on the lung

The shock wave action on the lung has been known for over 100 years from explosions and war injuries; it consists of bleedings (Clemedson 1956). Lung hemorrhage was also the earliest documented biological side effect of extracorporeal shock waves (Chaussy 1982). It was the most prominent side effect when shock waves were administered to dog gallbladders, although the lung was far away from the focus (Brendel and Enders 1983). The lung proved to be the most sensitive organ to shock waves as hemorrhages were already observed in mice after only 10 pulses of 2 MPa peak pressure (Hartman et al. 1990). In dogs, hemorrhages did not occur below a pressure of 2–3 MPa (Delius et al. 1987).

Hemorrhage extended from the lung surface several millimeters up to a few centimeters deep into the organ; obviously shock waves cannot cause isolated deep lesions because they are not propagated in the air-filled tissue. Histologically the alveoli, i.e. the 250 μm large, air-filled cavities where gas exchange occurs, were filled with blood. At lightly affected sites, the air spaces themselves stayed free of bleeding which occurred only within the 10–30 μm thin tissue bridges between alveoli, i.e. their septa. At heavily affected sites, these septa were so completely destroyed that no lung architecture could be recognized any more. Bronchi and large blood vessels which are comparably thick-walled structures were not affected.

The lung with its alveoli and septa can be regarded as a field of stabilized, thin-walled, interconnected gas bubbles. The positive pressure pulse is expected to interact directly with the alveoli, and there seems to be no necessity of a tensile wave to generate gas bubbles for shock wave-gas bubble interaction. This explanation is supported by the finding that fetal lungs which had not yet developed air spaces, did not show signs of damage even at exposure to pulse pressures of 20 MPa (Hartman et al. 1990). The lung's extreme sensitivity demonstrates that the pressure threshold for tissue damage is very low if suitable gas bubbles are present.

5.1.2. Shock wave action on the kidney

Shock waves have to pass the kidney parenchyma to reach a stone in the renal pelvis. Because of the ample use of kidney stone fragmentation, the effects of all types of shock wave generators have been examined at this organ (Newman et al. 1987; Abrahams et al. 1988; Delius et al. 1988b; Gunasekaran et al. 1989; Neisius et al. 1989; Recker et al. 1989). On their way to the pelvis, shock waves caused small, needlepin-like bleedings at the skin, the tissues of the body wall, and in the fatty tissue around the kidney. They are of no clinical significance. At the kidney capsule, bleeding has been detected in-between the layers of the capsular fibrous tissue. Within the kidney itself, two types of bleedings could be differentiated, diffuse bleedings and hematomas. Diffuse bleedings had a basically preserved kidney architecture at macroscopic inspection. They could be quite large, and extend from the site of shock wave entry all the way through the kidney (Fig. 7). Microscopic inspection revealed that they were caused by diffuse exit of red blood cells from the vascular lumen of capillaries and small veins into the surspace rounding, and also by filling of the small channels of the filtration system of the kidney with red blood cells. At electron microscopic examination, multiple small lesions of the venous and capillary walls were found as exit sites of the red blood cells (Karlsen et al. 1991). Massive bleedings, which are also called hematomas, were like blood blisters within the organ: a space completely filled with blood distended other structures, and even disrupted the normal kidney architecture. Hematomas were smaller than diffuse hemorrhages, their sizes ranged from a few millimeters up to around a centimeter (Fig. 7). They were usually caused by defects in the walls of medium-sized veins; defects of the walls of arteries were only rarely detected (Weber et al. 1992). Another prominent microscopical finding was the formation of blood clots in medium sized veins; they were typically associated with severe destruction of the wall of the respective vessel.

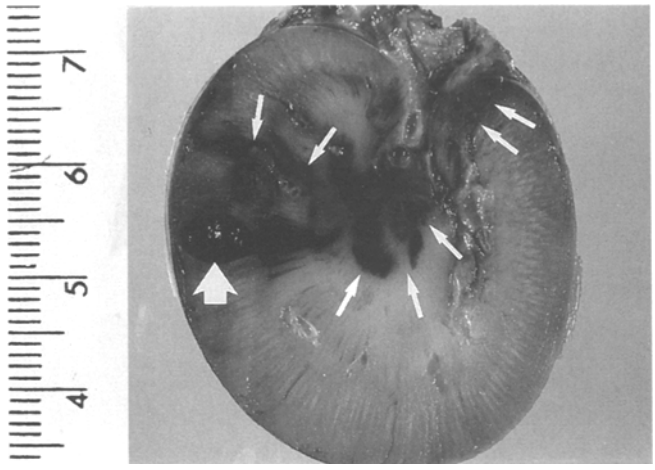

Fig. 7. Hemorrhages in the kidney after shock wave application. A hematoma (large arrow) is easily differentiated from diffuse hemorrhages (small arrows). Scale in cm

As expected, the bleedings in the kidney healed by scar formation. Some scars at the capsule were large enough to be visible with the naked eye; the loss of organ mass was only rarely large enough to generate a depression at the kidney surface. Histologically, many smaller scars were found within the kidney. Overall, the extent of scarring has

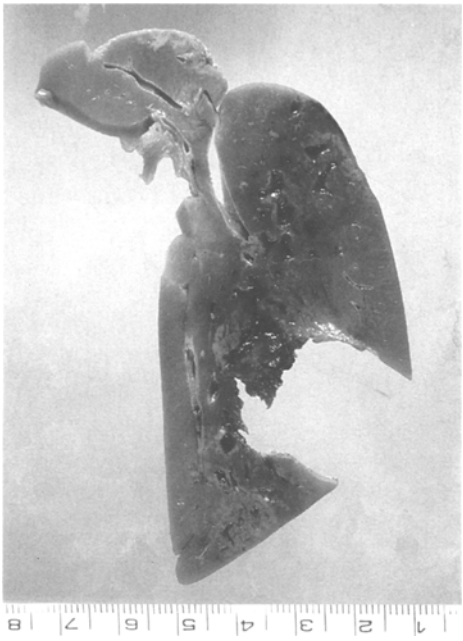

Fig. 8. Hemorrhages in the liver along the central ellipsoidal axis after shock wave application with an electromagnetic lithotripter. The shock wave entry site was at the bottom. Scale in cm (upper) or inch (lower) (from Delius and Gambihler 1992)

never been severe enough to suggest a substantial loss of renal mass which might hamper renal function. No long-term impairment of renal function has been documented.

5.1.3. Shock wave action on the liver and gallbladder

Since shock waves have to pass liver and gallbladder tissue to reach a gallstone their effects on these organs have also been well studied (Ell et al. 1989; Ponchon et al. 1989; Capdeville et al. 1990; Delius et al. 1990b). At the site where the shock waves entered the liver a 20–30 mm spot was generated with blood filled blisters and destruction of the capsular wall. Lesions within the liver were restricted to a 20 mm diameter area along the central lithotripter axis (Fig. 8) or – this was described with a piezoelectric lithotripter – to 20–30 mm spots within the liver tissue. Like in the kidney, they consisted of hematomas, and vessel wall damage and blood clots in those veins which transport the blood from the gut into the liver. Hematomas were maximally 20 mm large. In contrast to the kidney, no diffuse hemorrhages were observed; the reason for this difference is not known.

When shock waves were applied to the gallbladder, major parts of its wall were affected by diffuse bleedings. Massive bleedings into the bladder wall, destruction and even removal of the inner mucosal lining with bleeding into the bladder itself were additionally observed in a 10–20 mm diameter area in the focus.

5.1.4. Shock wave action on bone

In the first experiments of shock wave effects on bone, their action at the bone-cement interface and their influence on bone growth were examined. The former was studied because it was originally intended to apply shock waves for the removal of old bone cement from long bone shafts. This constitutes a major problem when an artificial hip with a cemented shaft has to be replaced. Studies were performed with freshly obtained bones, and initially, a loosening effect at the bone-cement interface was indeed reported (Weinstein et al. 1988); in a more recent experiment, however, no effect could be documented (Braun et al. 1992). It seems improbable that shock waves will ever be applied for bone cement removal since they have nearly no effect on the cement itself, and complete destruction of the large contact area between cement and bone – this is the site where shock waves act – would be a major trauma leading to the release of marrow into the circulation, a potentially fatal event. The influence of shock waves on bone growth during adolescence has also been examined (Yeaman et al. 1989). After exposure of a limb, they were found to induce shortening of the extremity because the growth plate, i.e. the thin zone of bone growth interposed between the end of a bone and its long shaft, had been bridged by bone trabecles, thus stopping further growth.

The predominant lesion from shock waves focused to bone was again bleedings (Delius et al. unpublished). They occurred at the outer bone surface, i.e. the periosteum, and in the bone marrow. Again, diffuse bleedings and hematomas could be differentiated . Two additional features were found, fragmentation of the fine bony trabecles within the bone with their displacement, and displacement of bone marrow from within the bone to the outside. The bone reacted to the shock wave trauma by intense apposition of new bone at its shaft, and as a result, it became considerably thickened. A joint in the high pressure area close to the focus was not affected by shock waves.

The displacement of bony trabecles and of bone marrow cannot be explained by a direct shock wave action. It can, however, be easily explained by the volume expansion from growing cavities within the marrow. Therefore, it points to the action of cavitation. Lesions from a direct shock wave effect should be expected at a place where the shock is reflected as a tensile wave. This is primarily the interface between solid bone and bone marrow, where the tensile wave should cause fracturing within the shaft. Since lesions of this type did not occur, no evidence was found for a direct shock wave effect. The absence of joint trauma can be explained by the missing vascular supply and lack of free fluid. At such places, cavitation cannot occur.

5.1.5. Shock wave action on the testicle and ovary

Exposure of testicles generated diffuse bleedings like in the kidney (Rüdiger et al. 1992). In another experiment, the appearance of the ovary was assessed after shock wave exposure, and oocytes were found intact (McCullough et al. 1989). A subsequent mating experiment did not reveal any abnormality of the litter.

5.2. Parameters determining tissue effects

For clinicians, it is important to know the physical shock wave parameters which determine the tissue effects. Matching these with the determinants of stone fragmentation might allow the design of treatment protocols with an optimized ratio between fragmentation and side effects.

5.2.1. Pulse energy

That tissue damage in the kidney was increased when the number of discharges was increased is not surprising (Delius et al. 1988b; Neisius et al. 1989; Recker et al. 1989). A high pulse energy had the same effect (Rassweiler et al. 1993). In the latter case, bleedings were observed directly under the renal capsule only with high pulse energy; at low pulse energy, they were not found even at high discharge numbers. Knowing the acoustic pulse energy makes it possible to administer the same overall acoustic energy with either a low number of high energy pulses or vice versa (it will be later mentioned that the fragmentation efficiency of both protocols is identical). Applying such a protocol in an experiment, tissue damage was more extensive with the low number of high energy pulses (Delius et al. unpublished). Therefore, use of a low pulse energy for treatment of most kidney stones seems of advantage. This is in accord with the currently observed trend to run lithotripters at a low pulse energy (Bierkens et al. 1992). Such protocols are however time consuming, and in practice tend to reveal lower rates of stone freedom. Obviously, a compromise has to be found between a pulse energy high enough to allow speedy and successful treatment, and an energy low enough to keep trauma and pain minimal.

5.2.2. Peak pressure and type of shock wave generator

Fragmentation efficiency, i.e. the amount of fragments generated per pulse, is a key parameter for the therapeutic application of shock waves. No investigation has so far been published in which the tissue effects of shock wave generators with a high and low peak pressure were compared at a similar fragmentation efficiency (and an identical number of pulses). There is also no comparison between different types of shock wave generators under this condition. When we investigated these questions, no difference was found between generators with 70 MPa peak pressure and those with 40 MPa (Delius et al. unpublished). Furthermore, tissue damage from electrohydraulic and electromagnetic shock wave sources was in a similar range. Therefore, peak pressure seems not to be a major determinant of tissue damage.

5.2.3. Administration rate

Shock wave administration is generally limited to 1–2 discharges per second. Since higher discharge rates could shorten the treatment time considerably, such protocols were investigated experimentally. Both shock wave application at a rate of 100 and 15 discharges per second revealed an increase in tissue damage (Delius et al. 1988c; 1990b; 1990c). An increase was also obtained when only two discharges were administered per second with the second discharge following the first one after 67 ms (Recker et al. 1992). It is explained by an interaction between shock waves at these fast administration rates which is not observed at the normal slow administration. Since the pulse duration is only in the range of approximately 10 μs, a residual effect must have persisted for 67 ms, i.e. for 6700 times the pulse duration. This can hardly be explained by a direct shock wave effect. The gas bubbles generated by shock waves in the body (see cavitation by tensile waves) provide a better explanation because they persist long enough to be encountered by the following shock. The increase in tissue damage at higher administration rate led to the model that biological shock wave effects are caused by shock wave-gas bubble interaction (Delius and Brendel 1988d).

5.2.4. Gas bubble injection

More recently, the tissue effects of shock waves were assessed under simultaneous injection of gelatine-stabilized air microbubbles via an arterial catheter (Prat et al. 1991a). The experiment should determine whether tissue damage was enhanced by gas bubbles as predicted by the shock wave-gas bubble interaction model. It revealed a dramatic increase by the microbubble injection. Moreover, lesions were not limited to the area around the central axis of the shock wave source, but abdominal organs at a larger distance were additionally affected. Gas bubbles occur in a lithotripter field only near its axis, and the wide spread of the lesions suggests that it is the bubbles that are the limiting factor for the generation of tissue damage. As described for the lung, low pressures seem sufficient to cause damage when suitable gas bubbles are present.

Recently, a piezoelectric device has been described which generated tensile waves more efficiently, thus eliminating the need for additional gas bubble injection (Prat et al. 1994). It was designed for maximal tissue damage in order to remove tumors, and tightly packed cavitation lesions were produced in the focus.

5.3. Effects on excitable tissues

5.3.1. Cardiac arrhythmia induction

The shock wave action on the heart is of interest because shock waves induce disturbances of the heart rhythm, i.e. arrhythmias. Triggering of the shock wave by the patient's electrocardiogram was instituted as a solution (Weber et al. 1984). Thereafter, induction of arrhythmias was a rare event, it stays however one of the most frequent reasons for treatment interruptions (Coptcoat et al. 1986). The induction of arrhythmias triggered attempts to use shock waves clinically in emergency medicine as an external cardiac pacemaker (Wirtzfeld et al. 1979). Their stimulating action was, however, too erratic and unreliable; longer pressure pulses of millisecond duration proved to be a more effective.

The pressure threshold for cardiac stimulation by shock waves was in the range of 5–10 MPa (Dalecki et al. 1991) or 1 MPa (Delius et al. 1994a). Fast shock wave administration at a rate of 100 Hz induced arrhythmias even far away from the focus where single pulses had nearly no stimulating activity. In analogy to the increased tissue damage by fast shock wave administration, the difference is difficult to explain by a direct shock wave effect; it points to the involvement of cavitation in arrhythmia induction as well. Maybe the heart is an extremely sensitive detector of cavitation. Since the cardiac muscle cells are electrically connected, excitation of a single fiber which would go unnoticed in other organs can spread over the whole heart and is registered as arrhythmia.

5.3.2. Nerve excitation

Nerves propagate a focal membrane depolarization, i.e. the local breakdown of the membrane potential, as an action potential, i.e. total membrane depolarization. They are therefore sensitive indicators of membrane damage. The action of shock waves on nerves has been examined many years ago in order to study the effects of high velocity projectiles hitting the human body (Wehner and Sellier 1982). During extracorporeal shock wave lithotripsy, every single pulse is experienced by the patient as a short-lasting pain sensation. This is direct evidence that lithotripter shock waves stimulate nervous tissue during their propagation in the body. The stimulation could be reproduced in vitro (Schelling et al. 1994). Yet, shock waves could only induce action potentials in nerves positioned outside the focus when gas bubbles were administered to the organ bath. Obviously, some form of shock wave-gas bubble interaction was required to generate action potentials by weak shock waves. In the focus, the generation of action potentials was inhibited by immersion of the nerves in polyvinylalcohol, a highly viscous fluid in which cavitation effects are suppressed. This suggested that cavitation was the mechanism of action potential generation; shock waves themselves had no effect on the cell membrane. As to the clinical situation, the experiments suggested that cavitation is the underlying mechanism of shock-wave related pain during lithotripsy. Pain reduction should therefore be achievable in lithotripters which cause less cavitation.

5.4. Effect on cells in culture

5.4.1. Cell killing

Shock wave administration to cells in suspension lyses, i.e. completely destroys into tiny debris, 5–95 % of the cells, depending on the number of discharges and their pulse energy, and causes cell death in another fraction. Generally, shock wave damage is acute, and the majority of cells which survive the shock wave exposure continue to proliferate at a near normal rate. Only in extreme cases was the proliferation transiently delayed (Gambihler et al. 1990). Different cell lines differ in their sensitivity to shock waves only by a factor of 2 (Brümmer et al. 1992). Shock waves acted about similarly on cells during different phases of the cell cycle (Oosterhof et al. 1989).

When multicell spheroids, i.e. balls tightly packed cells of 0.5 mm diameter, were exposed, the shock wave effect was reduced in comparison to a single cell suspension, and only the outer region of the spheroids was affected (Bräuner et al. 1989). Embedding in gelatine prevented damage completely (Brümmer et al. 1989). Even the mere clotting of blood or pelleting of cells before exposure reduced cell lysis (Laudone et al. 1989; Smits et al. 1991). Exposure in a pressure chamber at 10 MPa overpressure abolished it completely. All these experiments pointed to cavitation as mechanism of cell damage. Cavitation could also explain the increased shock wave effect in the presence of gas bubbles (Gambihler et al. 1992a), and at high shock wave application rates (Jones et al. 1992). Red blood cells can be used to quantify cell lysis simply by determining the amount of haemoglobin which is set free into solution (Laudone et al. 1989). The free hemoglobin has been found to increase linearly with the acoustic pulse energy (Delius unpublished). Obviously, cavitation-mediated effects are linearly related to the pulse energy.

Shear forces from fluid motion in the vicinity of shock wave-gas bubble interaction account for the vast majority of shock wave effects. Lithotripter shock waves have been shown to generate free radicals (Henglein et al. 1988), and to increase the intracellular concentration of an indicator dye for radicals (Suhr et al. 1991). It has been speculated that free radicals might contribute to cell killing. Their role is, however, not established since radicals from shock waves had little effect on cell proliferation when compared to a similar amount of radicals from ionizing radiation (Morgan et al. 1988). Moreover, the action of radicals in the medium was strongly influenced by the type of gas in solution while cell killing was not (Gambihler and Delius 1992a).

Recently, a piezoelectric shock wave source which generated stronger tensile waves (probably similar to the device described in 5.2.4) has been found to reduce the cell number by 99.9 % (Feigl et al. 1992). A similar result could only be achieved with a shock wave generator for lithotripsy when stabilized microbubbles were administered (Prat et al. 1991b) or a fluid-air interface was present.

5.4.2. Effects at the subcellular level

Severe alterations of the ultrastructure were noted at cells not lysed by shock waves. Electron microscopy revealed vacuoles in the cytoplasm, swelling of mitochondria, changes at the cell surface, and defects of the cell membrane (Russo et al. 1987; Bräuner et al. 1989; Kohri et al. 1990). They could easily explain why a fraction of cells was obviously dead after shock wave application. The threshold for shock wave damage at different subcellular structures differed (Steinbach et al. 1992). The cell membrane was the most sensitive organelle as pulses with an energy density of only $0.12\,\mathrm{mJmm^{-2}}$ disturbed its integrity; to achieve an effect at the cytoskeleton, mitochondria, and nuclear membranes, higher energy densities up to $0.5\,\mathrm{mJmm^{-2}}$ were required. It is not known whether cells which exhibited one or several of these alterations were vital or dead.

Shock waves can cause a transient increase in membrane permeability without leading to cell death (Gambihler et al. 1992). This was shown by entry of a dye which normally cannot enter living cells. Experiments with dextran molecules of different sizes revealed that even molecules with a relative weight of 2 million could enter the cytoplasm when present in the medium during shock wave application. This pointed to the generation of large pores in the cell membrane (Gambihler et al. 1994). They were short-lived because substances were only taken up when present during shock wave application. Under hyperbaric pressure, the uptake was completely abolished, demonstrating that cavitation was the mechanism of cell permeabilisation. So, there is obviously a spectrum of cavitation-induced effects which ranges from cell lysis at the upper end via cell death where the membrane permeability is permanently increased, to the transient increase in permeability at the lower end.

The increased permeability opens up the possibility to transfer even large molecules like genes and extremely toxic proteins directly into the cytoplasm of cells. This has already been accomplished (unpublished).

5.5. Effects on tumors

Any new treatment modality is examined for its effects on tumors. For shock waves, this was even done before tissue damage had been characterized (Russo et al. 1986); it stayed a major focus of research during the last years.

5.5.1. In vitro action

The shock wave action is similar at malignant and non-malignant cells (Brümmer et al. 1992). Many of the previously mentioned cellular and subcellular alterations have been examined at tumor cell suspensions. Tumors are often treated by combined therapeutic approaches, and it is therefore of special interest whether shock waves enhance the effects of other treatment modalities.

Shock waves enhance the action of selected anticancer drugs. In a study comparing five different substances, the action of only one was considerably enhanced, that of the others slightly or not (Gambihler and Delius 1992b). For an effect, the drug had to be present during shock wave exposure. Since it was the substance with the slowest entry into cells, the experiment pointed to a temporary increase in membrane permeability as a mechanism of shock wave action. Other mechanisms might be active as well since a slightly enhanced effect of another drug was noted even when it was added 24 hours after shock wave administration (Oosterhof et al. 1989). A similar effect was found by another group, however in only one out of a number of cell lines (Warlters et al. 1992).

5.5.2. In vivo action

The in-vivo effects of shock waves on tumors differed strikingly from those in-vitro. Histological examination of tumors revealed after shock wave application an increase in bleedings in and around the tumor; signs of a direct destructive action on tumor cells similar to the in vitro actions were not seen (Russo et al. 1987). In spite of the absent direct effect, shock waves had a pronounced effect on small tumors in rodents if they were administered under a suitable protocol. A single shock wave dose revealed mostly negative results, while repeated treatments with several thousand discharges administered on consecutive days induced growth delays lasting for days to weeks (Laudone et al. 1989; Geldorf et al. 1989; Weiss et al. 1990). Slowly growing tumors were more susceptible to treatment than fast growing tumors (Osterhof et al. 1990), and distribution of the discharges over multiple foci was even in very small tumors more effective than administering the same number of discharges to a single focus.

The mechanism of the shock wave action is probably their strong effect on the tumor microcirculation. Destruction of vascular walls (Hoshi et al. 1991) and a severe temporary reduction of the tumor perfusion (Gamarra et al. 1993) have been found. The shock wave action was enhanced by tumor necrosis factor, a drug which acts also on the microcirculation (Oosterhof et al. 1991).

The effect of several anticancer drugs was enhanced in vivo but the inhibition of tumor growth was not dramatic (Randazzo et al. 1988; Holmes et al. 1990; Hoshi et al. 1992). A previously drug-resistant tumor became sensitive to the drug by shock wave treatment (Weiss et al. 1994). The effect was explained by an increased permeability of the membrane of the resistant cells for the drug. Combining shock waves with hyperthermia seems attractive because the reduction of perfusion should help to keep the temperature up in the tumor; the combination has indeed been superior to the single treatment modes (Dellian et al. 1994).

The presence of a fluid-air interface behind the tumor in the shock wave path increases the shock wave action, and with its help, complete tumor eradication was achieved in small animal tumors (Weiss et al. 1990). This led to the postulate that the generation of different waveforms enhances the cavitation effects, and shock wave sources which differ from those used for fragmentation should be developed for tumor therapy (Delius et al. 1989). The effect of the first of these generators (Feigl et al. 1992; Prat et al. 1994) on solid tumors should be known in the near future.

6. Fragmentation effect of shock waves

Stone fragmentation is the principal medical application of shock waves. The limited fragmentation efficiency of todays lithotripters clearly hampers their use for the treatment of large kidney stones and gallstones. Increasing their efficiency without increasing pain or side effects is therefore a primary goal of shock wave research. The fragmentation effect can be assessed at human stones; yet kidney stones for in-vitro experiments are difficult to obtain since they are treated by shock waves, and the sensitivity of gallstones varies from one family, i.e. multiple gallstones of similar size and composition from a single gallbladder, to another, making comparative assessments difficult. Model stones of standardized composition play therefore an increasing role to determine the efficiency of a lithotripter.

6.1. Stone properties

A systematic study of the physical properties of human stones has only been started several years ago. Some of them will be mentioned in the following although their importance for the fragmentation process is still unknown. Even the question of whether kidney or gallstones which clearly differ in their mechanical and acoustic properties are easier to fragment has not been properly addressed.

6.1.1. Mechanical properties

A variety of mechanical stone parameters have been examined in kidney and gallstones. Microhardness testing of kidney stones revealed Knoop hardnesses of 210–990 MPa with calcium oxalate monohydrate stones being in the higher range and cystine stones in the lower range (Johrde and Cocks 1985a; Singh and Agarwal 1990; Zhong et al. 1992; Cohen and Whitfield 1993). When these values were compared to the ease of fragmentation by a lithotripter, no clear relation could be established (Dretler 1989). Generally, the microhardness of gallstones is about one order of magnitude lower than of kidney stones. Knoop hardnesses of 11–43 MPa were reported (Stranne et al. 1990), and Vickers hardnesses of 17 MPa for cholesterol and 34 MPa for pigment stones (Gracewski et al. 1992; Holtum 1993).

Both kidney and gallstones showed brittle behavior during fracture testing. As expected from their lower hardness, the fracture strength of gallstones was also lower. The strength of kidney stone cylinders was 0.5–1.5 MPa (Johrde and Cocks 1985b), and of gallstone cylinders 0.23–0.31 MPa (Stranne et al. 1990). A higher mean value of 2.1 MPa was found when intact stones were tested. The difference might be caused by the fact that most stones are composed of intact layers of a harder shell around a softer core. The tensile strength of gallstones was found to vary in a relatively narrow range of 0.4–1.0 MPa. The dynamic Young's moduli of elasticity were 8–30 GPa in kidney stones (Cohen and Whitfield 1993) and 4.6–7.1 GPa in gallstones (Holtum 1993); higher quasi-static elasticities were reported in those kidney stones which were more difficult to fragment (Zhong et al. 1993).

6.1.2. Acoustic properties

In kidney stones, velocities of sound of 1808–4651 m/s and impedances of $1.8–8.1 \times 10^6\ \mathrm{Nsm^{-3}}$ have been reported with attenuation coefficients of $2.5–10.4\ \mathrm{dBcm^{-1}}$ (Sing and Agarwal 1990; Zhong et al. 1993). Stones which were difficult to fragment had slightly higher velocities and impedances. In gallstones, velocities were only 1553–2456 m/s and impedances $2.12–2.87 \times 10^6\ \mathrm{Nsm^{-3}}$, while attenuation coefficients were higher at $4.3–16.2\ \mathrm{dBcm^{-1}MHz^{-1}}$ (Goedegebure et al. 1992; Holtum 1993). Generally, the impedance mismatch within a stone was too small to account for a significant wave reflection at interfaces, and in addition the high attenuation excluded multiple reflections. No correlation was found between the velocity of sound and stone hardness. Acoustic parameters of gallstones have so far not been related to the destructive effectivity of shock waves. Interestingly, the sonographic pattern of gallstones has been related to the success of lithotripsy (Dyrszka et al. 1991). When echoes were picked up from within a stone, there was a higher success rate than when only the surface was depicted as an echogenic rim. It has been suggested that the former stones had a purely radial architecture (Tsuchiya et al. 1986). Theoretically, this type of structure should promote the generation of long cracks since crack propagation is not interrupted at interfaces as in layered stones.

6.1.3. Chemical properties

At kidney stones, fragmentation has been successfully related to chemical stone composition. Cystine, calcium oxalate monohydrate, and especially brushite stones turned out in clinical studies to be quite difficult to fragment (Lingeman et al. 1986; Dretler et al. 1988; Klee et al. 1991). For gallstones, the question is not solved. Confusing results have been obtained when the cholesterol content was related to fragmentation. Two negative (Schachler et al. 1988; Schulte and Baron 1990) contrast to two positive reports (Zeman et al. 1991; Nitsche et al. 1993) which state however the contrary that stones with a high cholesterol need more or less shocks.

Kidney and gallstones are porous systems. Kidney stones have an exchangeable water content of 2–15 % (Cohen and Whitfield 1993) and gallstones of 20 % (Holtum 1993). Very low porosities of kidney stones were found in cystine and brushite stones, types which are difficult to fragment. Many gallstones contain a few microliters of gas which is amenable to compression (Vakil et al. 1991a).

6.1.4. Various target factors

What is probably known to most researchers from their initial experiments is the improved fragmentation of dry as compared to wet stones. The dramatic difference was recently illustrated in an experiment in which 22 discharges from a piezoelectric lithotripter initially fragmented dry stones whereas 27 times more, 610 discharges, were needed for the same effect in wet stones (Vakil et al. 1991a).

The influence of stone number at a similar overall volume was compared in several experiments. Two negative (Schachler et al. 1988; Arends et al. 1990) and a positive (Torres et al. 1990) result were found. Impaction of a model stone or just covering of its surface diminished the fragmentation rate (Vakil et al. 1991b; Parr et al. 1992).

6.2. Shock wave properties

In 1989 it was first reported that the acoustic energy which was needed to fragment a model stone by shock waves was the product of the pulse energy and the number of discharges (Koch and Grünewald 1989). It was similar when the pulses were focused by ellipsoids of different geometries (Mueller 1990). In contrast to the common opinion that time, peak pressure did not determine the fragmentation efficiency.

Similar results were obtained by other groups (Mishriki et al. 1992) who also established that the rise time of the shock front in the range of 70–210 ns had only very little influence on the shock wave effect (Granz and Köhler 1992). All experiments were performed with plaster model stones, but the results can be transferred to other model stones and gallstones (Delius et al. 1994b).

6.3. Mechanism of fragmentation

During the initial days of extracorporeal shock wave lithotripsy not much thought was given to the mechanism of stone fragmentation. The unquestioned concept then was that shock waves acted directly at a kidney or gallstone similar to their action at other materials. It was not backed by experimental evidence for the special case of a human stone. Shock waves were considered to fragment stones at the front side, the site of shock wave entry, by compressional effects, and at the exit site by the stress from the reflected wave, the Hopkinson Effect (Forssmann et al. 1977). It was the recognition of the importance of cavitation for the tissue effects which led to a rethinking whether cavitation could play a role in stone destruction as well.

Observation of gallstones during fragmentation in vitro revealed that breaking started at the anterior side where shock waves entered the stone (Delius and Brendel 1989; Holtum 1993). A variable amount of small fragments was eroded before the stone broke into major parts, leading to a classification of a chipping or breaking mode (Schulte and Baron 1990; Nitsche et al. 1993). A Hopkinson effect at the posterior side as in certain model stones was not found. This is in accordance with the high acoustic attenuation of gallstones which makes the appearance of this effect improbable.

That cavitation might be an important mechanism of stone destruction was first suggested by indirect evidence. Exposure of gallstones at 10 MPa static overpressure abolished fragmentation nearly completely (Delius et al. 1988d). Fragmentation was also suppressed when gallstones were exposed in glycerol at a viscosity 2300 times that of water. The same experiment suggested that the impedance mismatch was not a prerequisite for gallstone fragmentation, arguing further against a direct shock wave effect. Fragmentation was also suppressed in other media of high viscosity, agar-graphite gel (Zeman et al. 1990) and polyvinylalcohol (Delius et al. 1991). In the latter, fine fragmentation was completely absent but coarse fragmentation was still seen in a subset of stones. Since cavitation bubble motion could still be observed photographically in glycerol (Fig. 9), cavitation could still have been the reason for the fragmentation in viscous fluids.

A role of cavitation during stone fragmentation was recently supported by the finding of craters on surfaces of gallstones exposed in vivo (Vakil 1993). Surface cracks which were also found at these stones ran always through craters, suggesting a causal relation between crater and crack formation. In addition, observation of gallstones by diagnostic ultrasound during lithotripsy reveals regularly an increase of the stone's echogenicity which points to the generation of stable gas near the stone surface.

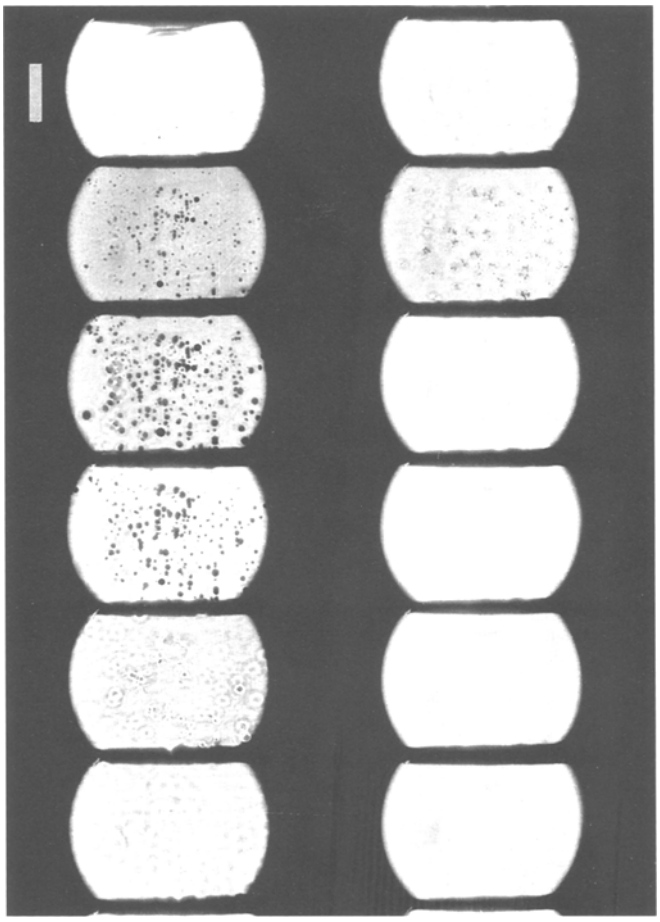

Fig. 9. Cavitation in glycerol (framing rate 10 000 images/second). Many bubbles are visible with maximal diameters of 3 mm. The first bubble oscillation takes 600 μs (same source as Fig. 4)

Direct visualization of gallstone fragmentation by high speed photography revealed more detailed insight into the course of events (Sass et al. 1991; Holtum 1993). The two major findings were the generation of large cracks at the stone surface and the generation of cavitation with subsequent crater formation at the shock wave entry site. The large cracks occurred early after the passage of the shock wave, long before the collapse of the major cavitation bubble. At framing rates of 5000–10 000 images/second, they were captured during the first image. The cracks oscillated at a starting frequency of 1.5 kHz but spatial separation of the stone fragments took 30–120 ms or more. Cavitation occurred on the central shock wave axis, and cavities persisted at the anterior stone surface for 0.6–0.7 ms. The bubbles collapsed onto the stone surface after assuming a ring-like shape, and in a sudden burst tiny fragments were removed from the point of impact.

The early occurrence of cracks before the collapse of the major cavitation bubble was considered to be evidence for their generation by a direct shock wave effect (Sass et al. 1991; Holtum 1993). Crater formation by cavitation at the impact site, a clearly cavitation-mediated event, was considered to merely facilitate crack formation without being a necessity (Holtum 1993). This was concluded from the finding that wrapping of a stone delayed crack formation but did

not prevent it. On the other hand have craters been observed at crack surfaces within the stone even before it broke apart into fragments, and it was concluded that cavitation occurs within stone cracks (Sass et al. 1991). Together with the previously mentioned intimate association of craters and cracks at the surface, this points to a possible role of cavitation during crack generation or propagation. What happens inside cracks is at present unknown. Cavitation in another narrow space, in thin liquid films, has recently been examined in a different context (Chen et al. 1992). Between moving surfaces, the inception of cavitation can be a much more violent event than the bubble collapse. This way, cavitation could even be involved in early crack propagation. A possible role of cavitation in the fragmentation process has also recently been supported by calculations of the compressive and shear loads from jets (Zhong et al. 1993).

Further evidence about the mechanism of stone breakage is expected from direct stress wave measurements in stones. They have so far only been performed in model stones (Gracewki et al. 1993). Cavitation is considered to be initiated by the tensile wave. As lithotripters without tensile wave have not yet been available, a simple method to examine the role of cavitation could so far not be employed.

Acknowledgement. The author wishes to thank Kerstin Jungnickel and Dr. Alfred Vogel from the Medizinische Laserzentrum Lübeck, Lübeck, FRG for their discussions and helpful comments as well as the high speed photographs. Many thanks to Dr. Andy Coleman, St. Thomas' Hospital, London, and Dr. W. Weber, Klinikum Großadern, who supplied figures from their publications.

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