SHOCK WAVES IN MEDICINE AND LITHOTRIPSY
**Shock Waves in Medicine**

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Extracorporeal generated shock waves were introduced for medical therapy approximately 20 years ago to disintegrate kidney stones. Today shock waves are the first choice for the treatment of kidney and ureteral stones. Meanwhile shock waves have been used in Orthopaedics and Traumatology to treat insertion tendinitis, non- or delayed unions, avascular necrosis of the head of femur and other necrotic bone alteration. Another field of shock wave application is the treatment of tendons, ligaments and bones of horses in veterinary medicine. The hypothesis of shock wave therapy for orthopaedic diseases is the stimulation of self-healing processes in tendons and bones. There are different shock wave devices in the market, which use different shock wave generating systems. Medical results with respect to success rates, number of shock waves per treatment and re-treatment rate differ significantly. At the moment it has not yet been established a correlation between physical parameters such as pressure, energy flux density or total focal energy and medical results. The shock wave itself generated by the various systems shows different properties and behaviour. Efficiency with respect to low re-treatment rates and low number of shock waves should be a request of shock wave systems. Different shock wave generation principles will be compared and analysed under this focus.

**INTRODUCTION**

Shock waves used in medicine were generated according to three different principles.

The electrohydraulic principle uses the tips of an electrode as a source. The electrode is placed in the first focal point of a semi-ellipsoid and a high voltage is switched to the tips of the electrode. An electrical spark is generated between the tips and the shock wave is released as a result of the vaporisation of the water between the tips. The spherical shock waves are reflected by a metal ellipsoid and focused into the second focal point, which in therapy is adjusted to the therapeutic volume inside the patient’s body. An essential characteristic of this principle is a real shock wave from the onset.

The electromagnetic principle uses a coil and a metal membrane placed opposite to it. A high current pulse is released through the coil, generating a strong varying magnetic field, which induces a high current in the opposite membrane. The electromagnetic forces accelerate the metal membrane away from the coil, creating a slow, low-pressure acoustic pulse in water. An acoustical lens is used to focus the wave. The amplitude of the focused acoustic wave increases in a nonlinear fashion when the wave propagates towards the focal point.

The third principle forms acoustic waves by the piezoelectric effect. A few hundred to some thousand crystals are mounted on a spherical surface. A high voltage pulse to the crystals causes them to contract, subsequent expansion generates a low pressure pulse in the surrounding water. The system is self-focusing, by the geometric shape of the sphere. Again, the shock wave is created by nonlinear and increasing amplitudes during the propagation of the wave to the focal point.

**Physical Parameters**

In Urology each lithotripter has a specific disintegration capability per shock wave for a certain energy level. The disintegration volume of a lithotripter could be estimated by the following equation:

\[ V = \varepsilon E n \]  

where \( V \) is the total disintegration volume, \( \varepsilon \) is the specific disintegration capability for a certain material and \( n \) is the total number of applied shock waves. In order to find a dose-effect relationship for extracorporeal shock wave therapy in Orthopaedics manufactures agreed to measure and to publish physical parameters of their devices. Physical parameters like pressure, energy flux density, energy and focal extent should be compared with medical treatment parameters and results to find an optimal dosage for shock wave therapy of orthopaedic diseases. The parameters are available and it seems quite clear that an easy correlation to only one parameter is not possible. Our literature review has revealed that electrohydraulic shock wave devices need a lower number of shock waves per treatment and a lower re-treatment rate to cure a patient compared to other generating principles. New clinical studies have shown that not only the treatment parameters but also the results differ significantly between electrohydraulic and electromagnetic or piezoelectric generated shock.
waves [1,2,3,4]. It is apparent that electrohydraulic generated shock waves are more efficient compared to other generating principles.

Table 1. Treatment parameters and results of clinical studies

<table>
<thead>
<tr>
<th>Indication</th>
<th>Device</th>
<th>SW*</th>
<th>Re-treatment rate</th>
<th>Success rate in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heel spur</td>
<td>OssaTron°</td>
<td>1500</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>EMSE</td>
<td>3800</td>
<td>1</td>
<td>not reported</td>
</tr>
<tr>
<td>Non-union</td>
<td>OssaTron</td>
<td>1000-6000</td>
<td>1</td>
<td>87.5</td>
</tr>
<tr>
<td></td>
<td>EMSE</td>
<td>4000</td>
<td>4 - 6</td>
<td>67</td>
</tr>
</tbody>
</table>

* Number of shock waves per treatment
° The OssaTron is an electrohydraulic orthopaedic shock wave device

**Shock wave characteristic**

A typical shock wave used in medicine can be described as a single pulse with a wide frequency range (up to 20 MHz), high-pressure amplitude (up to 120 MPa), low tensile wave (up to 10 MPa), small pulse width at –6 dB and a short rise time (< 10 ns). Folberth et al. [5] compared the pressure distribution in the focal region of two different shock wave generating systems, an electrohydraulic (Dornier HM3) and an electromagnetic system (Siemens Lithostar Plus). Shock waves generated by an electrohydraulic system show a specific shock wave behaviour in the centre of the focus, in the vicinity of the centre and far from focus centre. The essential characteristics, such as short rise time, small pulse width at –6 dB, high positive pressure amplitude and small tensile wave are fulfilled. This is different for an electromagnetic generated shock wave. The essential characteristics are only fulfilled in the focus centre and in the vicinity of the centre. This means electrohydraulic shock wave devices generate shock waves in a large focus volume, whereas electromagnetic shock wave devices have a real shock wave only in the focus centre and in a small area around the centre. Orthopaedic shock wave devices show the same behaviour [6].

Another difference between the shock wave generating principles is the ratio of the positive pressure amplitude and the tensile part. Electrohydraulic shock waves systems generate energy per shock wave mainly from the positive pressure amplitude while other systems generate it from the tensile part. The positive pressure and short rise time are responsible for the direct shock wave effect. The tensile part of a shock wave generates cavitation bubbles. These bubbles grow under the influence of the tensile wave [7].

Interfaces between two different materials with different acoustic impedance influence the shock wave travelling through the interface. Reflection, refraction at the interface and damping inside the material leads to energy loss of the shock wave. An essential characteristic of the electrohydraulic principle is the shock wave from the onset whereas other principles start with a slow, low pressure acoustic pulse. The very fast pressure transition of electrohydraulic generated shock waves (high pressure, short rise time) in a large focal volume causes very high tension at the interfaces, so that the structure of the material cracks. This effect depends on the plasticity of the material. The energy of the shock wave for the disintegration of kidney stones does not cause severe alterations in intact bone structures.

At present efficiency of orthopaedic shock wave devices has only been analysed with in vitro experiments. It is obvious that the situation is completely different in a water bath compared to the situation in vivo. Many interfaces with different acoustic properties are between the skin and the treatment area. Therefore the shock wave itself and the focus will change. The alteration of the shock wave and the focal volume could depend on the generating principle because of the discussed differences between electrohydraulic and electromagnetic or piezoelectric principles. Medical results such as treatment parameters and success rates have shown that electrohydraulic generated shock waves are more efficient and more successful compared to other generating systems (see Table 1).

**REFERENCES**

INTRODUCTION

SWL has been widely viewed as one of the most effective means of removing kidney stones since it was introduced in the early 1980’s. In contrast, views on the safety of SWL have changed as clinical experience with the protocol has increased. One of the first clinical reports on SWL expressed the view that shock waves “do not cause damage in passing through body tissue” (1), but less than a year later another laboratory reported renal injury in 63-65% of all SWL patients and that 30% of SWL patients experienced immediate post-SWL reductions of effective renal plasma flow (2). Since then, there have been many reports of SWL-induced renal injury and impaired function in human patients and experimental animals (3,4). The more current view on SWL-induced renal injury is that some degree of renal damage occurs with virtually every SWL treatment (5).

ANIMAL MODEL

Our group has used the female farm pig as a model system to determine the bioeffects of shock wave lithotripsy in that the pig kidney is similar in size, anatomy (including ureters) and function to the human kidney (3). Another advantage of the pig is that its body size allows us to position and treat the animal kidney in the unmodified Dornier HM3 lithotripter under the identically conditions used in clinical practice. In these studies, F2 of the lithotripter is focused on the lower pole calyx of the right kidney of juvenile pigs (6-7 weeks of age) and 2,000 shock waves are applied at 24kV. Females are used because both ureters could be catheterized, thereby permitting analysis of split renal function. The experimental design of our studies marks the first attempt to correlate structural and functional changes in the intact kidney following shock wave treatment. Each animal was subjected to a set of pre-SWL and 1- to 4-hour post-SWL evaluations, which included inulin and PAH clearances. At the end of the study, both kidneys were perfused with glutaraldehyde and routinely processed for morphological examination.

MORPHOLOGIC OBSERVATIONS

Gross examination of the kidneys revealed a large subcapsular hematoma at the site of F2 for every treated kidney. The site of injury within the renal parenchyma was localized to the region of F2, and extended the full height of the kidney (anterior to posterior surfaces) because this dimension was the same as the height of F2 (Figure 1). Thus, the lesion extends from the renal capsule to papillary tip, including the calyceal tissue region at F2 and then to the opposite renal surface. Those kidneys with a subcapsular hematoma always had a laceration that extended from the cortex to the hematoma, which can be clearly seen by in tissue sections (Figure 1). We
know from our other studies that by reducing the shock number to 1000 at 24kV, fewer kidneys showed a subcapsular hematoma.

Examination of the lesion sites by light and transmission electron microscopy revealed the morphological lesion to be unique, in that the physical forces of the pressure wave tore, lacerated and ripped through the wall of most veins and capillaries located in F2 producing primarily a vascular insult (6). Evidence of extensive endothelial damage in these veins was noted by a loss of endothelial cells and the immediate attachment of numerous polymorphonuclear cells (PMNs) and activated platelets to the luminal surface of these vessels depicting a vasculitis. Medium to small arteries also showed a unique injury. By light microscopy, injured vessels are identified by a characteristic swelling of the tunica media, which results in extensive narrowing of the vessel lumen. Sites of frank rupture are also seen. Destruction of the endothelium and vascular smooth muscle cells resulted in focal laceration sites causing hemorrhage into the intracellular spaces. Thrombus formation was often seen at these sites of breakage along with numerous platelets and PMNs. It is these vascular changes that may explain in part the intense vasoconstriction noted in the treated kidney.

Tubular and interstitial cell injury was also noted in the region of the vascular damage and was characterized by rips and tears that pass through the basement membrane and nearby cells resulting in irreversible cell necrosis. An immediate inflammatory response was also noted around these damaged tubules and interstitial cells. A process of tubulo-interstitial nephritis has been established immediately after SWL treatment. These site of injury over time become regions of scar tissue with a loss of tubules and vessels.

**FUNCTIONAL OBSERVATIONS**

Gross hematuria was consistently noted from the ureter of the treated kidney after the application of 200 shocks. The primary functional change found was a vasoconstrictive response in both kidneys (treated and untreated) (7). Renal plasma flow (measured by PAH clearance) was reduced as much as 60% in the treated kidney and by 35% in the untreated kidney 1-hour post-SWL (Figure 2). By 4-hours post-SWL the values for RPF in the untreated kidney were near baseline while a significant reduction was still noted in the treated kidney. SWL significantly reduced glomerular filtration rate (GFR) to a similar degree in both kidney over the same time periods (values not shown). Para-aminohippurate, a indicator of tubular function was only reduced in the treated kidney. These studies demonstrate that shock waves delivered at a number and intensity similar to that used to treat stone patients induces an injury that is predictable in size, focal in location and unique in the types of injuries (primarily vascular insult) induced. There is also a marked acute reduction in renal hemodynamics in both kidneys. Concern exists for the long-term consequences of these SWL-induced structural and functional changes.

**ACKNOWLEDGMENTS**

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**REFERENCES**

Correlation between the predicted stress field and observed spall-failure in artificial kidney stones treated by shock wave lithotripsy (SWL) in vitro

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We attempted to predict the failure of kidney stones due to the direct stress field of the lithotripter shock wave (SW). Numerical simulations of the acoustic field inside stones were carried out with a finite-difference time-domain (FDTD) code in a two-dimensional geometry. The code could model arbitrary shaped interfaces between the fluid and stone. Predictions from the code indicated that the peak tensile stress inside the stone was highly sensitive to the geometry of the distal surface of the stone; in particular curved surfaces produced a strong focusing effect. Focusing was weak for stones less than 3 mm in diameter.

INTRODUCTION

Shock wave lithotripsy has revolutionized the treatment of kidney stones and is used in approximately 90% of cases in the United States. Despite this there is no agreement in the literature as to the mechanism by which shock waves break kidney stones. There is also growing recognition that lithotripsy induces significant damage to the kidney.\cite{1} A better understanding of how shock SWs fragment kidney stones and how SWs impact tissue may provide a path towards safer more efficacious lithotripsy.

Five mechanisms have been proposed to explain SW comminution of kidney stones: Spallation; Superfocusing; Cavitation; Squeezing; and Fatigue. We have observed, in vitro, that stone destruction quickly progresses through a cascade of fragmentation from large pieces to fragments about 3-4 mm in diameter. The destruction of these fragments into 2 mm gravel (a size sufficiently small for a clinically positive result) can take a long time. We used a numerical model to study the effect of stone size and geometry on the mechanisms of spallation and superfocusing. We limited our study to assessment of tensile stress as the majority of kidney stones, like most brittle materials, are weakest in tension.

COMPUTATIONAL MODEL

Our model equation was the linear acoustic wave equation for lossy, inhomogeneous media:

$$\nabla^2 p - \frac{1}{c_0^2} \frac{\partial^2 p}{\partial t^2} = \frac{\nabla \rho_0}{\rho_0} \cdot \nabla p$$

Here $p$ is acoustic pressure, $c_0$ small-signal sound-speed, and $\rho_0$ density. We have neglected the presence of shear waves in the stone because for the geometries under consideration shear waves will have a limited impact on the tensile stress in the stones. We have also neglected the impact of nonlinearity and absorption as the propagation distances considered are short enough that the distortion from these effects will be weak. The equation was solved on a flat two-dimensional cartesian grid using a finite-difference time-domain (FDTD) algorithm that was second-order accurate in time and fourth-order accurate in space.\cite{2}

RESULTS

The focused shock wave was modelled as an incident plane wave (a reasonable assumption in the focal region) with a peak positive pressure of 40 MPa and a peak negative pressure -6.5 MPa.\cite{3} The acoustic properties were: water $c_0=1500$ m/s, $\rho_0=1000$ kg/m$^3$, and stone $c_0=3000$ m/s, $\rho_0=1700$ kg/m$^3$.

In Figure 1 we compare the prediction of the peak tensile stress in a square stone and a circular stone. In the square stone the incident compressive phase is inverted upon reflection from the distal surface and there is constructive interference with the trailing tensile phase of the lithotripter pulse. This results in a region of tensile stress near the distal surface of the stone which can result in failure by spall. In the case of the circular stone the incident shock wave is reflected (and inverted) as a converging wave from the concave distal surface. The peak tensile stress in this case is produced by focusing of the reflected wavefront, we refer to this as superfocussing, and leads to a localised region of tensile stress.\cite{4} Although the
resulting region of high tensile stress is different for the two shapes the peak tensile stress is of similar amplitude, in excess of 70 MPa.

**FIGURE 1.** Predicted peak tensile stress inside: (a) 10 mm square stone with a spall plane; (b) 10 mm diameter circular stone with a superfocusing spot.

Figure 2 shows the calculated peak tensile stress for smaller circular stones. In the 6.5 mm diameter stone the peak tensile stress has been reduced to 55 MPa and in the 3 mm stone the peak tensile stress is just 37 MPa - about half that in the 10 mm stone. The small region of tensile stress that occurs near the proximal surface is due to a subsequent reflection of the shock wave inside the stone from the proximal surface.

**DISCUSSION AND CONCLUSIONS**

We have shown that the region of high tensile stress is dependent on stone shape. Square stones, with a flat distal surface, produced a larger region of high tensile stress than a circular stone. For circular stones the amplitude of the peak tensile stress reduced as the stone diameter reduced. A threshold should exist where the tensile stress generated inside the stone is no longer large enough to fragment it. We speculate that multiple mechanisms may contribute to the initial break up of stones, and that when fragments become 3-4 mm in size those mechanisms that are dependent on stone size and shape (e.g. spall and superfocussing) are no longer effective, and a second mechanism, such as cavitation, is necessary to fully comminute the stone.

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**FIGURE 2.** Predicted peak tensile stress for a circular stone: (a) 6.5 mm diameter (b) 3 mm diameter.
The use of piezoelectric transducers array has open the possibility of electronic steering and focusing the beam to track the stone. However, due to the limited pressure delivered by each transducer (typically 10 bars), the number of transducers needed to reach at the focus an amplitude of the order of 1000 bars is typically of some hundreds elements. Here, we present a new solution that combines the use of time reversal method with a small number of transducers that generate low amplitude waveforms in a solid waveguide to obtained shock wave of very high amplitude in tissues located in front of the waveguide.

INTRODUCTION

Today extracorporeal shock wave lithotripsy is by far the method of choice to treat kidney and gall stones. It involves the use of large amplitude acoustic shock waves that are generated extracorporeally and focused onto a stone within the body. Lithotripters typically have a high focusing gain so that pressures are high at the stone but substantially lower in the surrounding tissue. The positioning of the patient alignment of stone with the lithotripter focus is accomplished with fluoroscopy or ultrasonic imaging. Focusing is achieved geometrically, i.e., with ellipsoidal reflectors, concave focusing arrays of piezoelectric transducers, or acoustic lenses. The shock waves utilised have amplitudes at the focus of the order of 1000 bars and duration of a few microseconds. Shock waves are typically fired at a 1 s pulse repetition rate.

The use of 2D arrays of piezoelectric transducers has open the possibility of electronic steering and focusing the beam in biological tissues. Tracking focusing procedures have also been studied [1]. The feasibility of a piezoelectric shock wave generator in which the focal zone is moved electronically to track the stone during a lithotripsy treatment using time reversal technique has been implemented and tested. However in such techniques, the number of transducers needed to reach at the focus an amplitude of the order of 1000 bars is typically of some hundreds elements. This is mainly due to the fact that today the piezoelectric transducer technology allows to deliver in front of a transducer an amplitude limited to 10 bars. The pressure generated by a transducer is proportional to the electric field applied between its two electrodes and to avoid breaking phenomena the value of the usual fields is limited to 2 kV/mm that corresponds typically to 10 bars.

Despite the spatial gain due to the spatial focusing, the number of transducers cannot be reduced if the beam has to be steered in attenuating tissues. As in time reversal technology, each transducer has its own electronic to record, time-reversed and retransmit the stone echo, the price of an electronic board of some hundred channels is yet very high and limits the commercial interest of such lithotripter.

In this paper, we propose a new elegant solution that combines the use of time reversal technology with a small number of piezoelectric transducers that generate low amplitude waveforms in a solid waveguide to obtained shockwave of very high amplitude in tissue or in a fluid located in front of the waveguide.

In this technique, we use the fact, that due to the time reversal invariance of the elastic wave equation in a lossless solid, for every burst of ultrasound diverging from a source and possibly multiply reflected by the boundaries of the waveguide- there exists in theory a set of elastic waves that precisely retraces all of these complex paths and converges in synchrony, at the original source, as if time were going backwards [2]. As the temporal dispersion of the waveguide increases, the time reversed wave is temporally recompressed with a stronger amplitude amplification. Typically, for a one microsecond initial pulse transmitted in the waveguide, if the signals dispersed and recorded by
some transducers have durations of some milliseconds, the time reversed waveform will refocus both in the
time domain and in space to generate a one 
microsecond pulse at the source position. Such a
spectacular effect allows to reach very high spatio-
temporal recompression and to obtain with a small
number of transducers the amplitude needed to break
stones. In this presentation, we study this technique
and we show that the technique give even more
spectacular results when we practice a 1 bit time
reversal operation instead of a classical 8 bit operation.

THE EXPERIMENT

The experiment is performed between a point
source in water and seven 8-mm piezo-electric
transducers fastened to a section of a 3.2-cm diameter,
50-cm length duraluminium cylinder. Both the source
and the transducers are linear and reversible : they
work in reception and in transmission. The central
frequency is 1 MHz with a 75% bandwidth, which
corresponds to a 5-mm central wavelength for
compressional wave in duraluminium. The bottom end
of the metallic cylinder is immerged in water at a
distance d from the source (d between 0-10 cm). Each
transducer is connected to an electronic circuitry
which consists of :
- two 15-MHz sampling-rate, 8-bit D/A and
A/D converters to receive the incident signal and
transmit the time-reversed signal.
- a memory which records the incident signal
sent from the source.
- a processor which creates a time-reversed
version of the incident signal.
According to these characteristics, classical time
reversal is then 8-bit time reversal. On the other hand,
during a 1-bit time reversal experiment, only the sign
of the time reversed signal is transmitted (+V if s(t)>0,
-V if s(t)<0, where V is the maximum amplitude of the
input signal)

After transmission of a pulse from the source
in S, the signal spreads in time because of many
reverberations on the interfaces of the solid
waveguide. The signal lasts more than 2000 µs, i.e.
around 1000 times the length of the initial pulse. In a
duraluminium sample, 2 ms corresponds
approximately to a 10-m distance, to be compared to
the 50-cm length of our cylinder. This means that
many round trips inside the cylinder are present in the
dispersed signal. We observe a remarkable time
compression on the initial source in S. This confirms
that the amplitude information which has been ignored
with 1-bit time reversal is not necessary to successfully
perform a time reversal experiment in a solid
waveguide.

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The Role of Renal Nerves in the Reduction of Kidney Blood Flow Observed After Shock Wave Lithotripsy (SWL)

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A reduction in renal blood flow (65\% in shocked kidneys, 33\% in contralateral unshocked kidneys) has been observed following delivery of a clinical dose of shock waves (SWs) (2000 SWs, 24 kV, Dornier HM3) to only one kidney. Using a porcine renal denervation model the role of renal nerves in blood vessel constriction after SWL was examined. Pigs (6 weeks old) underwent unilateral renal denervation. Nerves along the renal artery of one kidney were identified, sectioned and painted with 10\% phenol. After two weeks the pigs were anesthetized and renal function was determined using inulin and PAH clearance. The lower pole of the innervated kidney was then treated with 2000 SWs. Bilateral renal plasma flow (RPF) was measured 1 hour before and 1 hour after SWL. Both kidneys were then removed for analysis of norepinephrine (NE) content. Blood flow was reduced 50\% in the shocked kidney. However, the contralateral denervated kidney (NE levels 8.7\% of control) exhibited 0\% change in blood flow. The blunted vascular response in the contralateral denervated kidney suggest that the SWL pressure wave stimulates renal nerve activity in intact unshocked kidneys.

**INTRODUCTION**

The application of 2000 shock waves at 24 kV output energy to the lower pole calyx of young farm pigs damages renal tissue in the shocked kidney [1] and reduces renal plasma flow (RPF) and glomerular filtration rate (GFR) in both kidneys (Figure 1) [2]

There are at least two explanations for the reduction in RPF in the unshocked kidneys. In one instance, renal autonomic nerves may have been activated by the shock waves. Alternatively, there may have been the local or systemic release of a vasoconstrictor substance.

The present study investigated the role of renal nerves in regulating the vasoconstrictive response in the unshocked kidney by unilaterally denervating one kidney and bilaterally measuring RPF before and after SWL.

**METHODS**

Four 6-week-old anesthetized female farm pigs underwent aseptic laparoscopic denervation of one kidney. Visible renal nerves were dissected and cut, and the artery was painted with 10\% phenol. All incisions were then sutured closed and the animals were sent to recovery. Two weeks later, the pigs were reanesthetized and prepared for measurements of renal clearance. Catheters were placed in appropriate arteries and veins for infusions of fluids, measurement of arterial blood pressure, sampling of arterial blood, and bilateral collections of urine and renal venous blood.

**FIGURE 1.** Figure showing renal plasma flow before lithotripsy, and 1 and 4 hours after lithotripsy treatment. Animals were treated in a unmodified Dornier HM-3 with 2000 shock waves at 24 kV focused on the lower pole calyx of one kidney. Data are expressed as mean ± S.E. Asterisk indicates a significant difference from baseline at p < 0.05.

The clearance (C) and renal extraction (E) of p-aminohippurate (PAH) were determined for calculation of “true” renal plasma flow (RPF) for each
kidney. (RPF=C_{PAH} ÷ E_{PAH}), and the clearance of polyfructosan was determined as an index of GFR.

The innervated kidney of each pig was then targeted for application of 2000 shock waves at 24 kV (HM-3 lithotripter) output energy to the lower pole calyx. Timed collections of urine and blood were obtained from each kidney prior to and at 1 and 4 hours after SWL for determination of RPF and GFR. At the end of the study six 1-gram samples of cortical tissue were taken from each kidney (3 from each pole) for determination of norepinephrine (NE) content.

RESULTS AND DISCUSSION

The NE content of denervated kidneys was 1.2 ± 0.5% of that in the contralateral innervated kidneys on the day of the experiment. SWL produced the characteristic vasoconstictor effect in the shocked, innervated kidneys; i.e., RPF was reduced by more than 50% within 1 hour after SWL and had returned nearly to baseline 3 hours later (Figure 2). GFR was likewise reduced by nearly 50% at the 1-hour measurement, and was returning to baseline at 4 hours post-SWL (data not shown). In contrast, 3 of 4 denervated kidneys demonstrated no change in RPF or GFR at the 1-hour determination (Figure 2, RPF only). On average, neither RPF nor GFR in the denervated kidneys differed significantly from baseline over the 4-hour post-SWL course of the experiments.

These preliminary data support the hypothesis that the renal nerves mediate the reductions of GFR and RPF that typically occur in contralateral unshocked kidneys after the application of shock waves to the opposite kidney. Presumably, the shock waves may activate a sensory-afferent/sympathetic-efferent arc [3] beginning with sensory nerves in the shocked kidney and ending with efferent sympathetic nerves to the contralateral kidney.

It follows that sensory nerve traffic from shocked kidneys would activate sympathetic efferent nerves to both kidneys, contributing in part or in toto to the SWL-induced reductions of blood flow in shocked and unshocked kidneys alike. However, because RPF is ordinarily reduced to a greater degree in the shocked kidneys than in the contralateral kidneys, the greater vasoconstriction in the shocked kidneys may reflect the additive effects of sympathetic stimulation and locally-released vasoconstrictors. In any case, the present study was not designed to evaluate the role of nerves in the hemodynamic response of shocked kidneys to SWL.

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Localized cavitation detection in lithotripsy *in vivo*

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In order to determine if cavitation occurs within kidney tissue during shock wave lithotripsy (SWL) we devised a localization system in which our lithotripter source, two single-element transducers and an ultrasound scanhead were aligned confocal and orthogonal. B-mode imaging and fluoroscopy showed the position of the focus within the kidney. Hyperechoic clouds in the image indicated pockets of bubbles during SWL. A coincidence-detection algorithm and the confocal transducers made it possible to localize cavitation to within a 2x2x2 mm region. Cavitation was detected in pig kidneys during SWL. Following SWL, the tissue region that was SW treated and simultaneously interrogated was marked with a lesion produced by using the detection transducers as high intensity focused ultrasound (HIFU) sources. Thus, with this system in which we were able to correlate anatomical targeting (x-ray and ultrasound) with echogenicity, bubble collapse acoustic emissions, and a dual-source HIFU lesion we conclude that lithotripter SW's produce cavitation not only within the renal collecting system, but within kidney tissue as well.

**INTRODUCTION**

Cavitation is suspected to play a role in stone comminution and in collateral tissue injury during shock wave lithotripsy (SWL). [1, 2] Hyperecho indicative of bubbles has been seen in the collecting system and surrounding the kidney *in vivo* with B-mode ultrasound. [3, 4] Cavitation has also been detected *in vivo* with a single focused hydrophone[5, 6], however it is difficult to be sure detection was within tissue. Cleveland et al[7] devised and tested *in vitro* the use of 2 focused receivers and coincidence detection to better resolve the location of the cavitation. Here, we report on the simultaneous application of dual passive cavitation detection (PCD) and B-mode imaging to detect cavitation in kidney tissue during SWL.

**EXPERIMENTAL METHOD**

Experiments were conducted in a Dornier HM-3 electrohydraulic lithotripter (Dornier System GmbH, Germany). Two orthogonal single element listening transducers (1.1 MHz, aperture 10 cm, radius of curvature 10 cm) were mounted rigidly around the lithotripter reflector confocal with the lithotripter. Signals were high-pass filtered at 300 kHz, recorded on Tektronix TDS 744 oscilloscope (Beaverton, OR), and acquired and analyzed using LabVIEW software (National Instruments, Austin, TX, USA). Presented data have been rectified and smoothed to get the envelope of the signal. The lithotripter pulse first collapses bubbles then sets them into a growth that ends in collapse driven by the inertia of the surrounding fluid. The characteristic cavitation signal in SWL is two strong spikes, corresponding to each collapse, separated by time \( t_c \). The receivers are focused and most sensitive to a 2x14 mm cigar-shaped region. With two receivers and coincidence detection the region can be made considerable smaller to a volume of nearly 8 \( \text{mm}^3 \).

A 3-MHz phased array cardiac scanhead of a Sonosite 180 ultrasound-imaging machine (Bothell WA, USA) was mounted between the 2 receivers such that the image plane was parallel to the receiver axes. Images were stored on videotape and later analyzed with Adobe PhotoShop software (Mountain View, CA USA). Alternatively ring transducers were used with the imaging probe within them; however, the data reported in this paper is not with the ring transducers.

Anesthetized juvenile pigs (20 kg) were treated with SWL as described by Blomgren et al.[8] Lithotripter charging potentials were 18 and 24 kV. Not more than 2000 lithotripter pulses were administered and electrodes were replaced after every 1000 pulses.

The B-mode imaging and the fluoroscopy system of the Dornier HM-3 were used to align the pig kidney. The detection system and the lithotripter were focused
first in the collecting system and then in the tissue of the lower pole.

**RESULTS**

Hyperecho on the B-mode image was seen in the collecting system during SWL at both 18 and 24 kV. Bright flashes were seen with the first 5 pulses at 18 kV and within 1-3 at 24 kV. Within 10 pulses, the collecting system was filled with white. Very rarely (<1% of the pulses) a flash of white was seen in the tissue image.

Figure 1 shows dual PCD data collected in the fluid-filled collecting system. The signal amplitude in mV is plotted versus time. Lithotripter charging potential was 18 kV. Channel 1 is on top and Channel 2 is below. The second channel data is inverted in an effort to ease comparison. Both channels detected a strong signal at 70 µs when the lithotripter pulse arrived and at 405 µs. The average tc for N=250 pulses was 448±76 µs at 18 kV and 681±112 µs at 24 kV. Signals were detected 35% of the time at 24 kV.

Figure 2 shows dual PCD data collected in the lower pole at 18 kV. A spike at 70 µs and at 680 µs is evident on both channels. tc is 562±93 µs at 18 kV and 745±143 at 24 kV. Signals were weaker than in the collecting system and less common (N=250) 10% detection. There are more spikes between 70 and 300 µs. Spikes in this region varied but were very rarely coincident.

**CONCLUSIONS**

An ultrasound image-guided, localized cavitation detection and marking system was devised and tested. Cavitation was detected by dual passive cavitation detection (PCD).[7] Two focused receivers and coincidence detection allows us to detect within the tissue and within the fluid of the collecting system. Two charging potentials were tested 18 and 24 kV. In tissue the time tc, over which the bubbles grow and collapse, appears equal or slightly longer in tissue than in the collecting system fluid, 562±93 µs and 448±76 µs at 18 kV and 745±143 and 681±112 at 24 kV. PCD signals as well as hyperecho in the B-mode ultrasound image were detected much readily in the collecting system than in tissue.

The focal location and size could be assessed in vivo by using image-guided high intensity focused ultrasound (HIFU). In this way we could verify that refraction in the tissue did not greatly distort our alignment and that we were listening in tissue.

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**REFERENCES**


In Vitro Model of Shock Wave Lithotripsy (SWL) Produces Stone Breakage Equivalent to that Seen In Vivo

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Although in vitro model systems are used frequently in lithotripsy research, few attempts have been made to compare in vitro results directly with those in vivo. To determine if in vitro stone fragmentation correlates with that in vivo, gypsum stones were exposed to SWL in two systems: In vivo, stones were placed into pig kidneys and exposed to SW’s in an unmodified Dornier HM3 lithotripter. 400 SW’s (20 kV) were delivered at two rates. In vitro, stones were placed on plastic mesh inside a polypropylene tube, and exposed to SW’s in an HM3-like research lithotripter. At 0.5 Hz, SW’s in vitro yielded 280±34% breakage (increase in surface area, n=8), while in vivo breakage was 327±26% (n=6). At 2 Hz, in vitro breakage was 101±16% (n=20), while in vivo was 134±47% (n=7). Statistically, in vitro and in vivo effects did not differ, while the effect of SW rate was significant in both. Thus, with the in vitro system and lithotripters used here, both absolute stone breakage and rate effects were similar to what was observed in vivo.

INTRODUCTION

The progress that has been made in understanding the mechanisms by which lithotripter shock waves comminute stones and damage tissue is due in large part to work done in vitro. The in vitro situation offers greater control of experimental variables than can usually be done in vivo. For example, studies in which overpressure is applied to stones or cells being exposed to shock waves [1] would be difficult or impossible to carry out in anything other than an in vitro setting, and even simpler experiments can benefit from the control of extraneous variables that is possible with an in vitro approach.

This “in vitro advantage” is just as apparent in studies of stone comminution as it is in studies of cell or tissue damage. For example, the development of artificial stones has been important in providing experimental targets for lithotripsy that have less variability in fragility than is seen in natural stones [2]. Studying comminution of artificial stones in the in vitro setting offers the best combination for carrying out a well-controlled experiment.

However, it is also possible that the in vitro environment can fail to mimic the environment of the stone in vivo. While cavitation activity is generally high in samples exposed to lithotripter shock waves in vitro, the amount of cavitation activity in vivo could be much lower [3,4]. If this is the case, then conclusions made about, say, the role of cavitation in stone comminution could be in error if they are based solely on in vitro studies.

The work described here utilized a unique model in which artificial stones were implanted into pigs and exposed to lithotripter shock waves at two rates in a setting like that seen in the clinic. Identical stones were treated in vitro with the same dose of shock waves, and at the same two rates of shock wave delivery. Thus, the artificial stones—representing a reproducible target for testing comminution—were exposed to the same shock wave treatment under in vivo and in vitro conditions, providing an excellent comparison of the possible effects of environment on lithotripsy.

METHODS

Artificial Stones. Stones were cast in polystyrene multiwell plates using a commercial hydrated gypsum (Ultraceal-30, USG, Chicago, IL, USA). Polystyrene was dissolved away with chloroform, leaving artificial stones in the shape of slightly tapered cylinders (7.5 mm long by 6.5 mm mean diameter). Stones were stored under water and used within one week after casting.

In Vitro Study. Stones were placed in a plastic vial over a nylon mesh with 2 mm spaces and positioned at the focus of a research lithotripter that delivers a shock wave equivalent to that of the Dornier HM3 [5]. A plastic apron covered with polyethylene was used to catch the falling fragments. Following delivery of 400 shock waves (20 kV, 0.5 or 2 Hz), the retained and passed fragments were collected, spread out in a dish, dried, and scanned on a flatbed scanner. The projected surface area of the fragments was measured using appropriate thresholding, and the data expressed as the increase in area over that of an untreated stone.

Implantation and Lithotripsy of Artificial Stones In Vivo. Stones were implanted in both kidneys of female farm pigs (~45 kg) using a percutaneous access similar to that performed in percutaneous nephrostolithotomy for the removal of stones from patients. Upper pole peripheral calyceal puncture was performed with an 18 ga splenic needle and the tract was dilated using a Nephromax balloon and Amplatz sheath. A rigid nephroscope was used to visualize the renal collecting system and to guide one stone into a lower pole calyx, one stone per kidney. During a 2 hr recovery period urine
output returned to normal. Renal ultrasonography and fluoroscopy were used to confirm stone position. There was no occurrence of hydronephrosis, minimal perinephric fluid and no air within the collecting system. SWL was performed using a Dornier HM3 lithotripter (unmodified: 80 nF capacitor). Stones were targeted via biplanar fluoroscopy—initially and at every 50 shock waves. Shock waves were delivered uninterrupted; 400 shock waves per stone, 20 kV, 0.5 Hz or 2 Hz. Following lithotripsy, the urinary tract was removed en bloc and dissected in a retrograde manner to locate stone fragments that migrated from the kidney. Stone fragments were collected, debrided, placed in dishes and dried. They were then scanned on a flatbed scanner to determine projected surface area, as above.

RESULTS

In both in vitro and in vivo situations, there was a significant effect of the rate of shock wave delivery on stone fragmentation (Figure 1). It is noteworthy that there was no difference between the results found in vitro and in vivo, as determined by a two-way analysis of variance ($p<0.0001$ for rate of delivery; $p=0.2$ for in vitro vs. in vivo).

![Figure 1. Comparison of stone breakage at two rates, in vivo and in vitro. Both in vivo and in vitro show similar effects with rate, and stone breakage is not different between in vivo and in vitro. Each point represents one Ultracal-30 stone, treated with 400 SW's at 20 kV.](image)

DISCUSSION

Intuitively, it seems hard to imagine that the conditions that contribute to stone comminution in patients could be reproduced faithfully in vitro. First of all, the lithotripter shock wave is affected to some extent by passing through the body wall, being lower in peak pressure, with a longer rise time and larger focal region than what is measured in water [6]. Secondly, body fluids, including urine, are characteristically more difficult to cavitate than in vitro solutions, so the cavitation environment of a stone may be different in vivo [7]. Also, the presence of tissue can affect the cavitation activity and bubble behavior induced by shock waves [3,4]. In addition, the wide range of fragility of human stones makes any work with these targets inherently variable [2].

Only the last of these problems was controlled between the in vivo and in vitro conditions tested in the present study. The use of artificial stones provided a standard target for the two conditions. However, apparently the other parameters (shock wave and body fluid characteristics) were not critical for the comminution of these stones, as the results were identical between in vivo and in vitro.

One possible flaw in the methodology of this study is the inability to recover all the stone fragments after shock wave treatment in vivo. In the in vitro case, all the fragments are contained, and thus recovered after exposure to shock waves. In the animal, some of the smaller particles undoubtedly escaped with the urine. Indeed, on average only 75±3% of the stone dry weight was recovered. The difference that this would make to the projected area data in Figure 1 is not simple to predict, but it is certainly true that such an error favors better breakage in vivo than in vitro. Considering, as mentioned above, that some features of the lithotripter pulse are affected by in vitro conditions, this result is unexpected.

In summary, we have observed a close correlation between in vitro and in vivo results in assessing the influence of SW rate on stone fragmentation. This close correlation demonstrates that our in vitro test system gives a good approximation of stone breakage in vivo.

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Previous work has shown that shock wave (SW) lysis of cells occurs by both cavitational and non-cavitational mechanisms. SW’s can cause cell lysis, but it is possible that intracellular organelles could be damaged under conditions in which the cell is not ruptured. Such damage would likely not involve cavitation due to the high viscosity and lack of cavitation nuclei within cytoplasm. To assess the SW-fragility of intracellular organelles, unilamellar membrane vesicles were used as an in vitro model, and SW-induced damage was quantitated with and without high overpressure (>130 atm) to preclude cavitation. Membrane vesicles (~100 nm diameter, made by extrusion from egg phosphatidylcholine) were exposed to SW’s (1 Hz, 20 kV) in a research lithotripter with acoustic output similar to the Dornier HM3. SW-dependent vesicle lysis increased with SW number (p<0.001), with mean lysis of 0.12±0.02% at 400 SW’s (n=49 vials). (In comparison, red blood cells show >5% lysis with only 100 SW’s.) Overpressure did not protect against vesicle lysis and lysis with overpressure was not different from that at atmospheric pressure, 0.10±0.02% (n=10). In contrast, lysis of red blood cells is greatly reduced by overpressure. This suggests that when target dimensions are small enough, SW-membrane interactions are independent of cavitation bubble activity.

INTRODUCTION

There are at least two ways in which shock waves might cause damage to cells and tissues. Shock wave shear could tear tissue (or cells), and shock wave-bubble interactions in the form of cavitation and bubble expansion or subsequent bubble collapse could also lead to disruption of surrounding cells and tissue. In studies of red blood cells in vitro, it appears that both of these mechanisms play a role in shock wave-dependent cell lysis [1]. The lysis of red blood cells in suspension is significantly reduced by the application of excess hydrostatic pressure (overpressure). Overpressure reduces bubble formation and accelerates bubble dissolution [2]. Thus, reduced cell lysis in the presence of overpressure is consistent with the idea that much of the lysis (as much as 85%) is due to shock wave-induced cavitation.

However, these studies with red blood cells also showed that shock wave-dependent cell lysis was still significant, even when the overpressure was raised to a value greater than the tensile phase of the shock waves (>120 atm). At pressures this high, bubbles cannot expand, and therefore cavitation cannot occur. The persistence of cell lysis under this condition is strong evidence that shock wave shear is an important force for cell lysis.

These experiments were done with cells in fluid suspension. The result could well be different with an intracellular target. First of all, there is not likely to be any cavitation activity inside a cell—the gel-like environment would probably preclude that. Secondly, with either shock wave shear or cavitation, the stress put on the target will be related to the size of the target [3]. Just as a small piece of wood can float through a violent surf without being damaged, a small enough target should be unaffected by the shock wave. The purpose of this study was to test the effects of shock waves on vesicles of the same size as those present inside living cells (~100-150 nm).

METHODS

Vesicles were prepared by the extrusion method [4]. Egg phosphatidylcholine (Avanti Polar Lipids, Birmingham AL) was hydrated in buffer and passed multiple times through a polycarbonate filter of pore size 0.1 µm. Vesicles made this way are unilamellar and about 120 nm in diameter [4]. Carboxyfluorescein was included in the buffer, and just before use, vesicles were passed through a Sephadex G-25 column to remove extravesicular carboxyfluorescein. Lysis of the vesicles was measured by determining the level of carboxyfluorescein in the extravesicular fluid following treatment.

Exposure to lithotripter shock waves was done in a research electrohydraulic lithotripter that delivers a shock wave very similar to that of the Dornier HM3 [5]. Unshocked controls were used to determine baseline leakage of carboxyfluorescein from vesicles.

For experiments with overpressure, vials were mounted within a chamber that enabled pressurization to > 120 atm [6]. Briefly, this chamber has ends made of a plastic that allows the shock wave to pass virtually unaltered from waveforms measured in the free field.
RESULTS
Vesicles showed shock wave-dependent damage, as shown in Figure 1.

Figure 1. Lysis of unilamellar membrane vesicles by lithotripter shock waves. Shock waves were 20 kV, administered at 1 Hz.

Breakage of vesicles by shock waves was linearly dependent on shock wave number (data not shown). However, the percentage of vesicles lysed was much lower than we had previously observed with red blood cells. Vesicles lysed at a rate of about 0.03% per 100 shock waves, while red blood cells lysed at a rate of about 2.3% per 100 shock waves. The magnitude of difference is apparent in Figure 2, which also shows the effect of cell density on red blood cell lysis. The density of vesicles is much lower than that used for red blood cells, and this could have been a factor in the lower lysis rate seen in the vesicles. However, the effect of density on the red blood cells is actually in the opposite direction, so it does not appear that the low volume density of the vesicle preparation should play a role in the low lysis rate.

Figure 2. Lysis of unilamellar membrane vesicles and red blood cells by lithotripter shock waves. Volume concentrations of preparations are shown along bottom of figure.

To test whether vesicle lysis was dependent upon cavitation, shock waves were administered at overpressure, and results are shown in Figure 3. Note the overlap of data points in this figure. There was no significant difference between lysis of vesicles at atmospheric pressure and at 130 atm overpressure. This suggests strongly that the lysis of vesicles at atmospheric pressure was not due to cavitation.

Figure 3. Lysis of unilamellar membrane vesicles by lithotripter shock waves in the presence and absence of high overpressure.

DISCUSSION
Previous work with red blood cells showed that most of the shock wave-dependent lysis measured in these cells was eliminated by overpressure, showing that this lysis is strongly related to bubble action generated by the shock waves. The results with unilamellar vesicles does not show a pressure effect on shock wave-dependent lysis. This suggests that the lysis of vesicles is due solely to a non-cavitational mechanism, likely shear.

The low level of lysis in the vesicles—as compared to cells—does not appear to be related to the density of the preparations, as the density relationship seen in red blood cells goes in the other direction. Rather, the low level of lysis in the vesicles is consistent with a size effect predicted for the interaction of a membrane-bound object with diverging force vectors in a shock wave [3].

These results demonstrate that small biological targets—even those as small as intracellular organelles—can be damaged by lithotripter SW’s, and that this damage is independent of cavitation. Thus, it is feasible that subcellular organelles could be broken even within cytoplasm, a local environment in which cavitation is unlikely to occur.

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Alternative Pressure Waveforms for ESWL

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Basic research may still lead to safer, more efficient extracorporeal shock wave lithotripters. The modifications presented here are based on the fact that shock wave-induced cavitation is one of the most important mechanisms for stone fragmentation. Spatial and temporal dephasing of the shock front and the use of two, phase inverted, pressure pulses were studied using electrohydraulic and piezoelectric shock wave generators. Pressure measurements and stone fragmentation efficiency were compared using the new and the conventional systems.

INTRODUCTION

Despite the fact that ESWL (extracorporeal shock wave lithotripsy) has been the medical procedure of choice for patients with renal and ureteral calculi for more than twenty years [1], basic research is still necessary to define techniques that minimize tissue damage while improving treatment efficiency. Based on the results of previous investigations [2-5] we have been studying alternative focusing and shock wave generation systems for electrohydraulic and piezoelectric extracorporeal shock wave lithotripters.

Electrohydraulic lithotripters induce shock waves by electrical breakdown of water between two electrodes, located at the focus (F1) closest to a rigid para-ellipsoidal reflector. Shock waves are reflected off the reflector and concentrated at the second focus (F2). Since the patient is positioned with the calculus located at F2, shock waves enter the body, get focused on the stone, and fracture it [5]. It is the ellipsoidal reflector that concentrates the shock wave and permits it to be created extracorporeally. Treatment efficiency and tissue trauma depend on its material and design.

Piezoelectric extracorporeal shock wave lithotripters generate pressure waves by high voltage discharges sent to an array of up to 3000 piezoelectric crystals laid out on a metallic spherical segment. These waves get concentrated at the center of the segment. The crystals are covered with a flexible insulating material. As in electrohydraulic systems, water is used as a coupling fluid and patient positioning is performed by fluoroscopy or ultrasound imaging systems [5]. The devices presented here may also be used in the future for other medical applications like membrane permeabilization of cells in order to achieve effective macromolecule delivery in vitro and in vivo.

MATERIALS AND METHODS

Alternative reflectors for electrohydraulic lithotripters

Two composite reflectors, each obtained by combining two sectors of two rotationally symmetric ellipsoidal reflectors with different geometries were designed [6]. Reflector A is composed of two stainless steel sectors (major axes \(a = 278.0 \text{ mm}, a' = 313.0 \text{ mm}\); minor axes \(b = 156.0 \text{ mm}, b' = 166.4 \text{ mm}\)), having two F2 foci. Reflector B is obtained by combining one sector of a stainless steel rotationally symmetric reflector (\(a = 278.0 \text{ mm}, b = 156.0 \text{ mm}\)) and another sector of an ellipsoidal reflector made out of polyurethane foam (\(a' = 353.2 \text{ mm}, b' = 267.8 \text{ mm}\)). In this case, the foci F1 and F2 of both sectors coincide. Pressure measurements and kidney stone model fragmentation efficiency of the two novel reflectors were compared to that of a conventional reflector (unmodified Dornier HM3) on a research lithotripter [7]. Stone models were exposed to 250 shock waves generated at 22 kV (80 nF), placing them between F2 and F2’ (reflector A) or at F2 (reflector B).

Alternative electronic circuit for piezoelectric lithotripters

The discharge circuit of a Piezolith 2300 lithotripter (Richard Wolf GmbH), consisting of a capacitor charging system and a spark gap trigger unit was duplicated and connected in parallel to the piezoelectric crystal array. A specially designed pulse generator triggers both systems with a delay between 50 and 900 \(\mu\)s [8]. Due to this, two similar shock waves are generated. Pressure measurements at the focal zone were compared to those obtained using the conventional system. Fragmentation efficiency was
obtained exposing the models to pairs of shock waves having a delay of either 50 or 550 μs. The piezoelectric generator was operated at 7.5 kV. Spherical HMT (High Medical Technologies) kidney stone models, placed on a nylon mesh with 1.0 x 1.0 mm openings, were used for all experiments reported here and exposed at different positions to 250 shock waves. Pressure measurements were made with needle hydrophones (Imotec GmbH).

RESULTS

Amplitudes (peak positive pressure about 73 MPa) and waveforms generated by the conventional reflector are comparable to data published by other authors [5,8]. As expected, the wave reflected off A is the superposition of two compressional pulses (≈ 30 and 63 MPa), followed by a tensile phase (≈ 15MPa). The waveform produced by reflector B consists of a compressional peak (≈ 45 MPa), followed by a trough (≈ 13 MPa), about 50 μs ahead of a negative pulse coming from the soft (pressure-release) sector (≈ 18 MPa), followed by a positive pulse (≈ 36 MPa).

Pressure waveforms obtained with the dual-pulse piezoelectric system show two similar positive pressure peaks (≈ 37 MPa), followed by a negative phase (≈ 10 MPa), separated either 50 or 550 μs.

The mean weight of the dry residual stone fragments obtained with reflector A at F2’ was about 26 % less than the lowest value obtained with the conventional reflector. The best result achieved with the dual-phase reflector (B) was about 6% less than the best value measured with the standard reflector. Using the piezoelectric system with a delay of 550 μs improved the fragmentation efficiency about 12% compared to a delay of 50 μs. All differences reported here were statistically significant (one tailed P ≤ 0.01).

DISCUSSION AND CONCLUSIONS

Using reflector A, enhanced stone fragmentation did not occur at the region of maximum pressure, indicating that spatial and temporal phasing out of the shock wave plays a significant role in stone fragmentation and should be considered in designing ESWL reflectors. Reflector B also seems to be more efficient than the conventional reflector in breaking up HMT models. It is expected that this may still be improved by adjusting the delay between pulses. Reflectors A and B are supposed to be more efficient than standard ellipsoidal reflectors due to alternative compressions and rarefactions as well as enhanced cavitation. [3,4-6]. Analogously, triggering two, rather than just one, piezoelectrically-generated shock waves may increase lithotripter efficiency due to enhanced cavitation. Since cavitation bubbles are known to collapse about 250 μs after passage of the first shock wave, it may be convenient to trigger the second pulse with a delay between 200 and 300 μs.

This article is based on fragmentation in water bath set up’s using one type of stone model. It will be necessary to perform tests with different models and in vivo experiments with animals, to evaluate if the novel systems remain efficient and prove to reduce tissue damage.

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Visualization of temperature rise induced by high intensity ultrasound in tissue

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Temperature rise in excised bovine liver exposed to high intensity focused ultrasound was visualized experimentally and simulated numerically. An infrared camera, which records surface temperature only, was used to measure spatial temperature distribution. Two blocks of tissue were stacked, and their interface was placed along the axis of the ultrasound beam. After exposure to ultrasound, the upper piece was immediately removed, and the temperature on the axial plane was infrared imaged. Our theoretical model employs a KZK-type equation for the acoustic pressure field combined with a bioheat equation. It is shown that experiment and theory agree well on the location, shape, and dimensions of the heated region if the effective absorption coefficient of liver is 1.4 dB/cm/MHz. The higher value of absorption in excised liver compared to the known data for \textit{in vivo} or degassed tissue (0.35 – 0.7 dB/cm/MHz[1 – 3]) is hypothesized to be due to the presence of air bubbles.

\textbf{INTRODUCTION}

High intensity focused ultrasound (HIFU) creates localized heating deep in tissues which can be used to necrose tumors or cauterize vessels. Imaging of the temperature field in tissue is important for guiding HIFU treatment. Various methods can be employed, such as thermocouples, MRI, and ultrasound thermometry. However, thermocouples are local and invasive, MRI is expensive, and acoustic methods have poor accuracy and spatial resolution. Here we suggest a simple, but informative, laboratory method of imaging the temperature in tissue with a thermal camera. Temperature rise in excised liver induce by HIFU was infrared imaged and predicted numerically. Direct comparison of experimental images and numerical results is presented.

\textbf{EXPERIMENTAL METHOD}

Shown in Figure 1 is the experimental set-up. The HIFU transducer (2 MHz, 35 mm aperture, 55 mm radius of curvature) was mounted on the side of an acrylic box (6 x 9.5 x 6 cm). The box was lined with ultrasound transmission gel and gel was added for good coupling between the transducer and the tissue. The power output was calibrated by force balance. Bovine liver was used within 8 hours of excision. A large piece was cut to fill the box and then bisected at the half height of the box and transducer. Care was taken to avoid bubbles between the two tissue slabs by dampening the interface with water and gel. A tissue specimen was imaged with a Radiance 1 infrared camera (Raytheon TX USA) from above. Camera wavelength was 3-5 µm, and the penetration depth was less than 2 mm, so that only the surface temperatures could be measured. Experimental procedure was to heat the tissue for 5 seconds with 29 W of acoustic power. Then the top slab of tissue was immediately removed and the temperature field was recorded.
NUMERICAL SIMULATIONS

The acoustic field was modeled by the KZK-type equation that accounts for the combined effects of diffraction, absorption, and nonlinearity. A linearized version of the frequency-domain code was employed[4], as it was shown that nonlinear effects were negligible in liver for given acoustic output. The acoustic parameters of liver were taken as: density, $\rho_0 = 1214$ kg/m$^3$; speed of sound, $c_0 = 1614$ m/s; power law of absorption, $\eta = 1.266$[3]. Temperature field was computed by a bio-heat equation[5] using a finite difference scheme[4]. The thermal properties of liver were taken as: heat capacity, $C_v = 3.81$ J/cm$^3$/°C and thermal conductivity, $\kappa = 0.508$ W/m/°C [3]. Simulations were performed for various values of absorption from 0.35 to 1.4 dB/cm/MHz.

RESULTS

Numerical simulations predicted much higher temperature rise at the focal spot and quite different geometry of the temperature field than in experiment if computed with typical values of absorption given in the literature (0.35 – 0.7 dB/cm/MHz)[1 – 3]. It was hypothesized that absorption in ex vivo, not degassed liver is likely higher, because of exposure to air, than in vivo or in carefully degassed tissue. Air bubbles are strong nonlinear scatterers, so the radiated acoustic field contains higher frequencies with higher absorption rate, which may result in average enhancement of absorption[6]. It was found that the absorption 1.4 dB/cm/MHz provided a very good match between simulations and measurements for the entire 2D spatial distribution (the location, shape, and dimensions of the heated region), Figure 2. The spatial and temperature scales are the same for the two pictures. The transducer is on the right. Both predicted (a) and measured (b) distributions show a heated triangle (cone) that comes to a point close to the geometrical focus. Enhanced heating is seen close to the transducer, followed by a relatively less heating, and then by the highest temperature rise at the focal spot. In addition, two hot localized spots in are seen in measured image due to the presence of air bubbles. Little heating occurs on the far side of the focus which is typical for highly absorptive propagation.

CONCLUSIONS

A novel experimental method was used to visualize 2D temperature field in tissue. The method was shown to provide a clear image of the temperature distribution in tissue heated by ultrasound. Comparison of measured images with numerical modeling showed enhanced average absorption in excised liver due to reradiation from the air bubbles. Future experiments should include a direct measure of the attenuation in the samples and comparison with the degassed samples.

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Small Aperture Piezo Sources for Lithotripsy

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To improve the handling and to reduce the costs of piezoelectric transducers used in lithotriptors new transducer designs with two layers of piezoelectric elements are investigated. Using this construction principle the generated pressure near the transducer surface can be significantly raised up and relevant properties of the sound field can be preserved. 3-D FEM simulations are used as a design tool. Simulation results and measurements are compared to each other and are in high agreement. The double layered design allows a reduction in the transducer diameter and in the number of needed piezoelements to about 50%.

SINGLE LAYERED AND DOUBLE LAYERED PIEZO TRANSDUCERS

In extracorporeal lithotripsy of renal, salivary or gall stones peak pressures of about 100 MPa should be generated in the focal region. This can be achieved by self focusing single layered (SL) piezoelectric mosaic transducers with diameters of about 50 cm and 85° apex angle, driving the piezoelements close to their electromechanical limits. A multilayer design however can substantially increase the initial pressure at the radiating surface and therefore allows to reduce the transducer in diameter and in the radius of the radiating spherical cap simultaneously and in the number of needed piezoelements as well. Transducers with two layers of piezoelements on both sides of a supporting spherical cap (DL) were investigated. In Figure 1 the principle of the design is shown.

Figure 2 represents the driving electrical pulses, whose delay times are adjusted so that the wave front emitted from the back layer coincides with the wave front generated by the front layer on the radiating side.

3-D SIMULATION & VERIFICATION

Parameters as piezo design, mounting cap and electric excitations influence the transducer performance [1]. To investigate a mosaic structure, 3-D calculations are advisable. We used CAPA software for FEM 3-D simulations in time domain. Considering the symmetric structure the hexagonal mosaic was primarily reduced to an acute-angled triangle containing at its acute angle a 30° sector of a single cylindrical element. It can be shown easily that the whole mosaic can be calculated using this basic element and appropriate boundary conditions at the symmetry planes.

FIGURE 1. Structure and operation principle of a plane transducer with two layers of piezoelements.

FIGURE 2. Voltage pulses applied on back layer and on front layer (bold).

FIGURE 3. Comparison of simulated and measured pressure responses at a distance of 50 mm on the axis of a 10 cm diameter test transducer, double layer of hexagonal mosaics with cylindrical elements.
The FEM analysis shows complicated transient behaviour of a single piezoelement and its surrounding epoxy material following the voltage pulse excitation. The radiating surface gets curved and bent, contains elastic wave movements and does by far not act like a piston source. Some cm of travel path however are sufficient to form a regular uniform wave front due to the superposition of the pressure pulses of the mosaic.

In Figure 3 the calculated pressure signal for a hexagonal plane and infinite double layered mosaic of cylindrical piezoelectric elements is shown and compared to pressure measurements done at a plane test transducer of 10 cm diameter with a fibre optical hydrophone at 50 mm distance on axis.

**COMPARISON SL50 VS DL50**

For comparison a SL with 50 cm diameter (SL50) and a double layered test transducer with 26 cm diameter (DL26) are investigated by fibre optical measurements in water tanks. Using the driving voltage as parameter we see from Figure 4 that the SL50 design reaches 100 MPa focal peak pressure at 2.3 kV whereas the DL26 design needs 3.2 kV for it. This is due to the fact that SL50 has a longer propagation distance from surface to focus than the smaller and more curved DL26, the SL50 type thus profits from nonlinear steepening of the wavefront since both apex angles are about equal. The DL26 design also is appropriate for lithotripsy reaching peak pressures of over 130 MPa.

In Figures 5 and 6 the peak pressure distributions are shown. The driving voltages are adjusted to produce about comparable focal pressures. The DL26 produces a larger (-6dB) focal volume, a fact that is not only due to the smaller aperture but also to its shorter pulse propagation path which influences the nonlinear steepening of the pressure and leads to a less sharp focusing property. This can be regarded as an advantage of the DL26 system since during lithotripsy it becomes more easy to position the targets (stones) into the therapeutically relevant focal pressure zone. The enlarged focal volume may also be advantageous in orthopedics and pain therapy, where larger therapeutical volumes but lower focal intensities are preferred.

**REFERENCES**


The Application of Low-Energy Shock Waves to One Renal Pole Prevents Hemorrhagic Injury Induced by High-Energy Shock Waves in the Other Pole

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Two thousand shock waves (SWs) applied at 12 kV to one renal pole cause no hemorrhagic lesion but induce renal vasoconstriction. We examined the lesions appearing in upper and lower poles of kidneys after 2000 SWs at 12 kV to one pole followed immediately by 2000 SWs at 24 kV to the other pole. Three anesthetized pigs received 2000 SWs (Dornier HM3) to the lower pole at 12 kV and 2000 SWs to the upper pole at 24 kV. Four pigs received 2000 SWs at 24 kV to one pole. Renal hemodynamics were measured before and 1 hr after SWs. Shocked kidneys were fixed, sectioned and digitized for visual analysis. Similar reductions of renal blood flow occurred in shocked kidneys receiving SWs to both poles or only to one pole. Kidneys treated first at 12 kV sustained little to no hemorrhagic injury, other than scattered petechii, in either pole. By comparison, massive hemorrhagic injury occurred in kidneys treated only in one pole.

INTRODUCTION

High-energy shock waves (24 kV) administered by shock wave lithotripsy (SWL) predictably injure renal tissue and reduce both glomerular filtration rate (GFR) and renal plasma flow (RPF) (1,2). The size of the injury normally increases both with increasing shock wave voltage, being minimal at 12 kV (3,5), and with increasing numbers of shock waves. (4,6) Shock-wave induced reductions of RPF, however, appear to be independent of voltage (3).

When we treated each renal pole in succession with 2000 shock waves at 24 kV in earlier experiments, the second application caused less injury and bleeding than the first. This protective effect may have resulted from the renal vasoconstriction normally induced by a single dose of shock waves. Moreover, since shock waves administered at 12 kV reduce RPF but cause little to no tissue injury (3), vasoconstriction caused by treatment of one pole at 12 kV might protect the other pole from injury caused by 2000 shock waves at 24 kV. The present studies tested that hypothesis.

METHODS

Two groups of female pigs, 6 weeks old, were anesthetized (ketamine, 15-20 mg/kg i.m. for induction, then isoflurane 1-2% and oxygen 100% for maintenance) and prepared for renal clearance experiments. Catheters were placed in a peripheral vein for infusion of fluids, a femoral artery for measurement of blood pressure, both renal veins for measurement of the renal extraction of p-aminohippurate (EPAH) and in both ureters for bilateral urine collections. Three 15-minute baseline collections of urine and mid-point blood samples were followed by the application of 2000 shock waves at 12 kV to the lower pole of one kidney followed immediately by 2000 shock waves at 24 kV to the upper pole of the same kidney (Group 1, n=3). Group 2 (n=4) received 2000 shock waves at 24 kV only to the lower pole of one kidney. Two more sets of three 15-minute clearance collections were obtained at 1 and 4 hours after SWL (unmodified Dornier HM3 lithotripter). The focal zone for the shock waves (F2) was fluoroscopically aligned with the targeted region with the aid of contrast media injected into the renal pelvis.

Steady-state concentrations of polyfructosan and PAH were infused i.v. throughout the experiments. Urine and plasma samples were analyzed by standard colorimetric methods. Clearances of polyfructosan and PAH were calculated as estimates, respectively, of GFR and RPF. EPAH was used to calculate “true” RPF (TRPF = PAH clearance ÷ EPAH). The criterion for statistical significance was p<0.05. The experimental protocol was approved by the Institutional Animal...
Care and Use Committees for the Indiana University School of Medicine and Methodist Hospital of Indiana. At the completion of the clearance studies, all animals were prepared for vascular perfusion of both kidneys (7). The kidneys were then embedded and sectioned. Computer-assisted segmentation techniques were applied to serial sections of the kidneys to determine lesion sizes (8).

RESULTS

The application of 4000 shock waves to one kidney (2000 to each pole) of Group 1 pigs and 2000 shock waves to one pole of Group 2 kidneys caused similar maximal reductions of GFR and RPF in both groups. $E_{\text{PAH}}$, which reflects the integrity of renal tubular secretion, was reduced only in the shocked kidneys of Group 2.

Lesion sizes were quantified in the shocked kidneys from 3 pigs in Group 1 (12/24 kV) and 4 pigs in Group 2 (24 kV only). In Group 1 kidneys, mean lesion size, calculated for the entire kidney, was about one-sixth that of the lesions seen in the shocked poles of Group 2 kidneys even though the kidneys of Group 1 received twice as many shock waves as did the kidneys of Group 2 (Figure 1).

FIGURE 1. Size of hemorrhagic lesions produced in each of 3 kidneys from pigs treated with successive applications of low- and high-energy shock waves (12 and 24 kV) first to the lower pole, and then to the upper pole (open bars). The mean for this group (shaded bar) is compared with mean lesion size in pigs treated only with high-energy (24 kV) shock waves to one renal pole (solid bar). The asterisk denotes a statistically significant difference; vertical bars denote standard error of the mean.

DISCUSSION

The first application of 2000 shock waves at 12 kV to one renal pole in Group 1 produced little to no evidence of hemorrhagic injury. The subsequent application of 2000 shock waves to the opposite poles of those kidneys at 24 kV likewise produced little evidence of injury (Figure 1). A dose of 2000 shock waves applied alone at 24 kV would ordinarily have been expected to produce lesions amounting to about 6% of the functional renal mass (Figure 1). Thus, the initial application of low-energy shock waves to one pole clearly seems to have protected the opposite poles of those kidneys from injury and bleeding.

The mechanism by which pretreatment of one renal pole with low-energy shock waves protected the opposite pole from subsequent damage by the high-energy shock waves is not immediately clear from these studies. We know from previous studies (3) that low-energy shock waves reduce RPF, presumably by causing vasoconstriction. Since the lesion caused by SWL is hemorrhagic, it seems reasonable to suggest that vasoconstriction induced by the first application of shock waves limited the bleeding, and hence the development of the lesion, caused by the subsequent application of high-energy shock waves.

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Holographic interferometric quantitative study of pulse laser induced underwater shock waves and cavity bubble

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Paper reports a quantitative study of underwater shock waves and cavity bubbles induced by direct irradiation of pulse laser beam. Energy source was a Q-switched Ho:YAG laser. The laser beam was focused and transmitted through an optical fiber. Double exposure holographic interferometry was used for flow visualization. The whole sequences of underwater shock waves generation and propagation were observed. The laser interaction produced micro plasma, which drove spherical shock wave in water and followed by formation of a vapor cavity. By shaping the optical fiber’s surface to a hyperboloidal contour, an effective laser focusing and stronger underwater shock waves were achieved. The micro shock waves produced by this method have potential to be applied for precise medical procedures.

INTRODUCTION

For applying shock waves to precise medical procedures like cerebral thrombolysis, generation of underwater micro shock waves plays an important role [1]. Such sensitive application makes limit on usage of conventional underwater shock wave sources like shock wave reflection and focusing over half-ellipsoidal cavity, so-called Extracorporeal Shock Waves ESW [2], or micro explosives [3]. In the present study a Q-switched Ho:YAG laser and a 0.60 mm glass optical fiber are used. Advantages of this method over previous shock wave sources are two order of magnitude reduction in focusing area if compared with ESW and elimination of product gases of micro explosives. Nakahara and Nagayama [4] studied underwater shock waves emanated from an optical fiber by pulse Nd:Yag laser input using shadowgraph technique. Their qualitative study limited to visualization of shock waves at its early stage. The present research aims to clarify quantitatively; (a) process of the shock wave generation by direct laser beam irradiation; (b) effects of the optical fiber’s end configuration on the shock wave strength; (c) growth and collapse of the generated cavitation bubble; and (d) structure of heat induced flow in front of the fiber.

EXPERIMENTAL METHOD

Energy source was a Q-switched Ho:YAG laser (Nippon Infrared Industries Co., Ltd.) with 91±10% mJ/Pulse energy measured at the end of a 0.60 mm diameter glass optical fiber, pulse duration of 200 ns, and wavelength of 2.1 µm. The laser beam was transmitted through the optical fiber. Double exposure holographic interferometry was used for quantitative flow visualization. Figure 1 shows a schematic diagram of the optical set-up. The light source was a holographic double pulse ruby laser (Apollo Laser Inc. 22HD, 25 ns pulse duration, 1 J/pulse). The first laser exposure was carried out before triggering of the Ho:YAG laser and the second exposure was synchronized with the propagation of the shock wave at the test section with a proper delay time. The whole sequences of the spherical shock wave generation and growth of the induced cavitation bubble were successfully observed.

RESULTS AND DISCUSSION

Figure 2 shows infinite fringe interferograms of generation and propagation of the underwater shock waves from roughened end of the optical fiber. Figure 2a, 4 µs after shock wave production, shows a 5.9 mm radius spherical shock wave in water. The shock wave generation associated with the laser breakdown in the water. The laser interaction produced micro plasma in the water and heated the liquid. The plasma drove spherical shock wave in water. This process followed by formation of a high temperature vapor cavity. In front of the optical fiber in Fig. 2a the vapor bubble of about 0.5 mm dia. is observed and fringes next to it
indicate the high temperature of that zone. Shock wave propagation through the optical fiber produced a conical precursor wave, which is clearly observable in Fig. 2a. In this figure first shock wave followed by another shock with 0.5 mm radial distance and shock front had a fold shape. This process is related to Ho:YGA laser irradiation from the optical fiber. A random or rough end surface of the fiber can produce diffuse transmission of the laser beam and separate focal areas with different energies. This made a delay for distinct plasma and shock wave generations. Figure 2b, at 100 µs, shows cavitation bubble of 2.3 mm dia. The high temperature in front of the optical fiber resulted in higher growth of the vapor cavity in that direction. Figure 2c, at 300 µs, shows the cavitation bubble after its first collapse. By that moment secondary cavity is produced which is observable in front of the optical fiber in Fig. 2c. Heat induced flow was vanished after 100 ms. Figure 2d, at 3.2 µs, shows a uniform spherical shock wave with 5.1 mm radius from a hyperboloidal shaped optical fiber. In this figure, by effective laser focusing, a stronger underwater shock wave is produced.

CONCLUSIONS

A Q-switched Ho:YAG laser and an optical fiber were used for production of underwater spherical micro shock waves. Using double exposure holographic interferometric quantitative flow visualization its generation process and propagation were observed. Growth and collapse of the induced cavitation bubbles were clarified. The weak shock waves produced by this method have potential to be applied for precise medical procedures such as revascularization in neurosurgery [5].

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**FIGURE 2.** Infinite fringe holograms of underwater shock waves and cavities: (a) 4 µs, (b) 100 µs, (c) 300 µs, from roughened end surface of optical fiber; and (d) 3.2 µs, from hyperboloidal optical fiber.
Shock waves induced antigenic modification on renal cell carcinoma

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The objective of the present study was to determine whether shock waves could modify antigenic pattern on the surface of surviving cells after shock wave exposures. Suspended human renal carcinoma cells (TOS-1) were exposed to 1000 focused under water shock waves at 16 MPa over pressure in the focal region. Expression of a cytosolic antigen (monosialosyl galactosyl globoside) was analysed with double staining flowcytometric assay (Propidium iodide/FITC) before and after the exposures. Expression of the antigen was increased on the surfaces of the treated cells and remained detectable during 4 hours after the exposures; however, it gradually declined to the control level by elapse of time. The increased intensity was mostly found on the surfaces of live shrunk cells; a newly generated population of the cells following the shock waves. The quantitative data obtained from flowcytometric analysis was confirmed by immunoelectron microscopic images, which revealed displacement of the antigen from the cytoplasm toward the cell periphery. According to the obtained results, shock waves were able to enhance the MSGG expression on the surfaces of the surviving TOS-1 cells, which in normal condition was negative or low expressed. The modification might be a preferred target for shock-wave-based approaches to cancer therapy.

INTRODUCTION

Combination of shock waves with substances acting on the cellular level has been reported as the most effective method than mono-therapy [1,4]. Therefore, detailed knowledge of shock wave-tumour interaction at the cellular level is important in order to develop the most effective combination.

The adverse immune reactions following Extracorporeal Shock Wave Lithotripsy (ESWL) raised the question whether shock waves could change antigenic pattern on the surfaces of cells in general and tumour cells in particular [3,6].

In this preliminary study, effects of shock waves on the expression of a cytosolic glycolipid antigen, monosialosyl galactosyl globoside (MSGG) was investigated, in-vitro.

MATERIALS AND METHODS

Cultured human renal carcinoma cells, TOS-1, suspended in PBS (2x10\textsuperscript{6} cells/ml) were transferred into polyethylene tube whose bottom was cut and sealed with a thin polyethylene film. The suspension was positioned in the focal region of a piezoceramic generator dish and was treated with 1000 shots at maximum over pressure of 16 MPa (Fig. 1). To measure the antigen intensity on the surfaces of intact cells and to prevent interference from dead cells a double staining flowcytometric assay (Propidium Iodide / FITC) was used.

An indirect immunoperoxidase technique [5] was applied for sub-cellular localisation of the antigen by immuno-electron microscopy.

Control cells (-SW) were treated in the same ways except for the shock waves.

FIGURE 1. Schematic diagram of the experimental set up.
RESULTS AND DISCUSSIONS

The flowcytometric assay of the –SW cells revealed that MSGG is a cytosolic antigen with almost no expression on the surfaces of the cells. The expression pattern was changed on the surfaces of the treated cells (+SW), as is shown in Fig. 2. The increased intensity was mostly found on the surfaces of shrunk cells; a newly generated population of the cells following the shock waves. The modification remained detectable during 4 hours after the exposures and gradually declined to the control level by elapse of time.

FIGURE 2. Histogram plot of the antigenic intensity on the cell surfaces.

The quantitative results were confirmed by immuno-electron microscopic images, as shown in Figs. 3a-b. The immuno-stained antigens were found as small dark spots non-uniformly scattered in the cytoplasm of the control cells (Fig. 3a). After the shock waves, this distribution pattern was changed to a membrane pattern in which the antigens were predominantly concentrated in the membranous structures close to the outer surfaces of the cell (Fig. 3b).

Regarding to the cases of autoimmune diseases, It is assumed that the phenomenon might be a common but reversible one in-vivo, however in some individuals it might be irreversible or lead to a permanent surface modification.

FIGURE 3. Histogram plot of the antigenic intensity on the cell surfaces: a) before the shock waves; b) after the shock waves. (Original magnification 15,000X)

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Basic Research of Laser-induced Bubble/Shock Interaction Applied to Revascularization of Cerebral Embolism

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In previous study, we successfully revealed that the detonation of silver azide pellets weighing a few mg produced shock wave/bubble interactions in water. The interactions were found to form liquid-jet and effectively penetrate layers of artificial thrombi. In this paper, laser-induced bubble and shock wave driven by micro-explosive were interacted to produce the liquid-jet. Pulse Ho:YAG laser beams transmitted through 0.6 mm dia. optical fiber. Phenomena were observed by high-speed camera. As a result of this, the collapse of bubbles impinged with micro shock waves induced micro-water jets, which penetrated readily artificial thrombi for several mm in depth. And laser-induced water-jet released from narrow catheter was also effective to penetrate the thrombi.

**INTRODUCTION**

Cerebral infarction has to be treated within 6 hours after onset. Extension of blood vessel with balloon catheter is usually conducted for recanalization in present. However, success rate of the treatment is about 75% and serious side effect often appears because of using large amount of fibrinolytics. Development of fibrinolysis on cerebral artery is promoted.

Liquid-jet can be produced by shock wave/bubble interaction, and the liquid-jet can penetrate thrombi. Instead of the former method, application of liquid-jet to cerebral embolism was worked out, and the effect of liquid-jet on revascularization was certified in vitro experiments \cite{1}. For approach of this technique to clinical field, trial liquid-jet generators were developed and in vitro experiments to break artificial gelatin thrombi with the trial device were carried out.

**EXPERIMENTS**

**Shock/Bubble interaction liquid-jet**

Figure 1 is schema of liquid jet generator caused by shock wave/bubble interaction. Shock wave and bubble is produced by micro-explosive and laser irradiation going through optical fiber, respectively. Irradiated laser is pulse Ho:YAG laser (Nippon Infrared Industry Co. Ltd, 350msec pulse width, 350 \textsuperscript{10%}mJ/pulse). Wavelength of Ho:YAG laser is 2.1 mm, which is near to the absorption wave length of water \cite{2}. The optical fiber has 0.6 mm core diameter. Explosive used to generate shock wave was AgN\textsubscript{3} pellet. The explosive is ignited by YAG laser. Weight of the explosive was 25 \textsuperscript{13%} mg. Shock wave propagated through the gap between two tubes in Fig. 1. 10% gelatin artificial thrombus was inserted to 4 mm inner diameter glass tube. The glass tube is in front of the liquid-jet generator. Experiments were conducted in water container, which has 110mm length and 110mm breadth and 130mm height. 5 mm acrylic plates were put on the both side of the container for visualization. The glass tube is at the center of the container. Liquid-jet produced in the glass tube and breaking process of the artificial thrombus by liquid-jet were observed by high-speed camera (SHIMADZU Co. Ltd, prototype ISIS-CCD).

**FIGURE 1.** Schema of shock/bubble interaction liquid-jet generator

**Jet catheter**

Figure 2 is cross section of trial jet catheter. Optical fiber was inserted to the catheter (2mm diameter). Rapid bubble expansion in narrow tube induces the water-jet going out from the catheter. There was distance between exit of the catheter and tip of the fiber, the distance is described "stand-off distance D" after this. D is variable parameter. Pure water flew in the catheter. Flux was 150 ml/sec. The catheter was inserted into the glass tube, and tip of the catheter was contacted to the surface of the artificial thrombus. Condition of experiments was same as above-mentioned experiments, and breaking process of the artificial thrombus by jet catheter were visualized by high-speed camera.
RESULTS AND DISCUSSIONS

Shock/Bubble interaction liquid-jet

Figure 3 is time-resolved photographs of liquid-jet production process and penetration of liquid-jet into the gelatin thrombus. Laser-induced bubble becomes maximum size at 800msec and vanishes at 1.2 msec after irradiation in our previous study [3]. So that explosive ignition time was changed around at 800 msec after laser irradiation. Fig 5(b) is one of result. Penetration depth into the artificial thrombus reaches to 4.2 mm from this time-resolved photos. Penetration with only laser irradiation was 2.25 mm in our previous study [3]. This means that liquid-jet has more effective characteristics on cerebral embolism. Figure 4 shows the relationship between ignition time and jet length. This graph indicates that shock wave should interfere to maximum laser-induced bubble

Jet catheter

Figure 5 shows the relationship between parameter D and penetration depth. This figure indicates that maximum penetration can be obtained under D=13-15 mm condition and that strength of jet can be controlled readily by changing D. These results also display that the trial jet catheter can only break thrombi mechanically but also increase area of contact surface between fibrinolytics and thrombi. From this effect, decreasing of fibrinolytics can be expected. The concept of the catheter can be considered a kind of drug delivery system. Besides, shock wave can be created in collapse process of bubble. There is possibility to apply to recanalization of lime-thrombi.

CONCLUSIONS

Manufacture of trial device on cerebral embolism and verification of the device was carried out in vitro, and following conclusions are obtained.

1. Liquid-jet caused by interaction between laser-induced bubble and explosive-induced shock wave is more useful than simple laser irradiation on cerebral embolism. Penetration depth is about twice as simple irradiation. Explosive should be ignited at the time when bubble becomes maximum size.

2. Trial jet catheter in present study can make large penetration into gelatin artificial thrombi. Penetration is about four times as simple laser irradiation. The catheter has potential of application to cerebral embolism.

REFERENCE

Cavitation Promotes Spall Failure of Model Kidney Stones Treated by Shock Wave Lithotripsy *In Vitro*

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Studies were conducted to assess the role of cavitation and spall in the breakage of artificial stones in vitro. Hydrated gypsum cylinders held in a mesh basket (free to move) fragmented readily when treated (400 SW’s, 20 kV) at atmospheric pressure. Treatment with a higher dose of 1600 SW’s, but, at overpressure (>130 atm) sufficient to preclude cavitation, dramatically reduced damage. These stones remained intact and showed no erosion, but upon examination by micro-computed tomography, some stones were seen to exhibit internal fractures. Overpressure could have suppressed the fracture failure of these stones. Also, stone movement within the vial likely created shot-to-shot variation in the location of the tensile stress necessary for spall. With this in mind stones were stabilized by holding them with water-saturated gauze. These stones treated at atmospheric pressure failed by spall within 300SWs. The gauze did not prevent cavitation, as the SW-entry surface of the stone showed erosion. When a Mylar disk was held directly against the SW-entry end of the stone the stone showed no erosion and did not spall. Moving the mylar proximal to the gauze did not prevent spall. These observations suggest that in this particular in vitro system, cavitation bubble collapse at the surface of the stone contributed to failure by a spall mechanism.

INTRODUCTION

A variety of mechanisms have been proposed to explain how lithotripter shock waves (SW’s) break kidney stones. There is good evidence to show that enhancement of tensile stress due to SW reflection off the distal side of the stone can cause it to fail by spall [1]. Cavitation in the fluid surrounding the stone, particularly at its proximal surface also has been shown to contribute to stone fragmentation [2,3]. It has been proposed that cavitation bubble collapse could create secondary shock waves that, like the focused SW of the lithotripter pulse, contribute to tensile stress within the stone [4,5]. Here we report observations with in vitro systems using artificial stones in which cavitation appears to promote spall failure.

EXPERIMENTAL METHODS

Artificial Stones: Stones (cylinders 7.5 mm long by 6.5 mm dia) were cast from Ultrapal-30 gypsum [6] (United States Gypsum, Chicago, IL) and stored in water.

Lithotripter: SW’s were administered using a research electrohydraulic lithotripter that has been demonstrated to produce acoustic output comparable to an unmodified Dornier HM3 lithotripter [7]. For all in vitro configurations stones were positioned at F2 and treated at 20 kV, 0.5 Hz.

Shock Wave Exposure at Overpressure: Stones contained within a mesh basket were positioned inside a chamber in which excess static pressure (overpressure) could be applied. The overpressure chamber had acoustic windows that allowed transmission of the SW with minimal attenuation and virtually no alteration in waveform [8]. Overpressure well-in-excess of the amplitude of the tensile phase of the SW (~80-100 atm) could be achieved (overpressure >130 atm possible).

Stones Stabilized for SW Exposure: Stones were held upright in water by surrounding them with water-saturated cotton gauze (Figure 1). Gauze was wrapped around the stone, which was then fitted into a plastic tube filled nearly to the mouth with such gauze. At this point one end of the stone remained uncovered. A cushion of gauze was placed over this end, held in place with a threaded cap. For some stones, a 6.5 mm disk of 5 mil Mylar was laid against the end of the stone, held in place by the gauze cushion and cap. The cap had a Mylar window (5 mil) and the distance from the window to the stone was 5 mm.

Analysis of Stone Damage: Stones were analyzed by visual inspection and by micro-computed tomography using a Scanco-20 research CT scanner (Scanco, Zurich).

RESULTS AND DISCUSSION

Stones held within a 2 mm mesh basket and treated at atmospheric pressure with 400 SW’s broke into numerous fragments, many of which could pass through the mesh. Stones treated with up to 1600 SW’s, but at extreme overpressure (>120 atm) did not break into frag-
ments, but some of these stones did show faint cracks. In previous studies we have shown that overpressure suppresses cavitation [8,9]. Overpressure in the range of 1-3 atm eliminates cavitation in water as assessed by high speed photography and passive cavitation detection [10]. Foil targets which show pitting when exposed to SW’s at atmospheric pressure, show no pitting when treated with SW’s at 120 atm [8]. Thus, overpressure eliminates cavitation, but might also suppress the failure of a stone by spall. That is, since spall is the failure of a material under tension, application of overpressure in excess of that tensile stress could very well stabilize the stone and keep it from breaking up. Because overpressure might interfere with spall we looked for another means to control cavitation. We reasoned that if the cavitation that erodes the proximal surface of a stone involves bubble activity intimately associated with the surface of the stone it might be possible to physically interrupt the growth of these bubbles, thus preventing their forceful collapse. We devised a setup in which a thin sheet of Mylar could be pressed against the stone. Stones stabilized by gauze (but with no Mylar disk pressed against stone surface) showed proximal erosion and spall—often with complete transverse breakage (Figure 2, left). When Mylar was in place, the stones showed no erosion of their proximal surface, and these stones did not spall (Figure 2, right). To test whether the Mylar disk interfered with transmission of the SW we tested placement of the disk next to the cap. Stones treated with this configuration showed proximal erosion and spall.

In summary, these observations suggest that both cavitation and spall contribute to stone fragmentation. Spall can occur in the absence of cavitation, but at least as seen with this particular in vitro system, spall failure is dramatically enhanced when cavitation occurs at the proximal face of the stone.

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REFERENCES
Slowing the Pulse Repetition Frequency in Shock Wave Lithotripsy (SWL) Improves Stone Fragmentation In Vivo

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In clinical lithotripsy shock waves (SW’s) are often delivered at rates as fast as 2 Hz. This may not give the best stone breakage, as in vitro studies have shown that slowing the SW rate (<2 Hz) improves stone fragmentation. We tested the effect of SW rate on stone comminution in vivo in a new animal model. Artificial stones were inserted into both kidneys of ~45 kg pigs via percutaneous access. SWL was performed (Dornier HM3, 400 SW’s uninterrupted, 20 kV, 2 Hz or 0.5 Hz), and stone fragments were collected and sieved through 2 mm mesh. The percent of stone weight lost (particles <2 mm), was greater in stones treated at 0.5 Hz than with 2 Hz. Thus, slowing the SW rate improved the efficiency of stone fragmentation in vivo. One explanation for this effect is that bubbles along the SW axis were more numerous with faster rate. These bubbles might interfere with SW propagation; however, in vitro measures with a PVDF membrane hydrophone showed no effect of SW rate on arrival time or amplitude of the positive pressure pulse. Thus, the acoustic mechanism for this SW rate effect on stone comminution has yet to be determined.

INTRODUCTION

The current trend in clinical SWL is to treat patients at the relatively fast rate of 2 Hz. In vitro studies have shown that SW rate is a factor in stone fragmentation and that human and artificial stones break better at slower rates [1]. We sought to test the effect of SW rate on stone comminution in vivo using a new animal model. Here we report that slowing the SW rate improved the efficiency of stone breakage in vivo. To better understand the acoustic mechanisms responsible for this effect we collected waveforms at two rates (0.5 and 2 Hz) using a PVDF membrane hydrophone and assessed for differences in SW parameters including arrival time, and maximum amplitudes and areas of the compressive and tensile phases.

EXPERIMENTAL METHODS

Implantation of Artificial Stones Via Percutaneous Access: Hydrated gypsum stones (Ultracal-30; 7.5 x 6.5 mm) were implanted in both kidneys of female farm pigs (~45 kg) using a percutaneous access similar to that performed in percutaneous nephrolithotomy for the removal of stones from patients. Upper pole peripheral calyceal puncture was performed with an 18 ga splenic needle and the tract was dilated using a Nephromax balloon and Amplatz sheath. A rigid nephroscope was used to visualize the renal collecting system and to guide one stone into a lower pole calyx, one stone per kidney. During a 2 hr recovery period urine output returned to normal. Renal ultrasonography and fluoroscopy were used to confirm stone position. There was no occurrence of hydronephrosis, minimal perinephric fluid and no air within the collecting system.

Shock Wave Lithotripsy: SWL was performed using a Dornier HM3 lithotripter (unmodified: 80 nf capacitor). Stones were targeted via biplanar fluoroscopy—initially and at every 50 SW’s. SW’s were delivered uninterrupted; 400 SW’s per stone, 20 kV, 0.5 Hz or 2 Hz. Control stones were implanted but not treated.

Harvest and Quantitation of Stone Fragments: The urinary tract was removed en bloc and dissected in a retrograde manner to locate stone fragments that migrated from the kidney. Stone fragments were collected, debrided, sieved through 2 mm mesh, and dried. Fragments retained by the mesh were weighed.

In Vitro Assessment of SW Rate on Lithotripter Waveform: Studies were performed using a research electrohydraulic lithotripter with the same acoustic output as the Dornier HM3 lithotripter [2]. Series of >100 SW’s were fired (20 kV, 0.5 Hz or 2 Hz) and waveforms collected at F2 using a PVDF membrane hydrophone (Ktech, Albuquerque, NM, USA) that we shielded with a film of RTV silicone sealant.
RESULTS AND DISCUSSION

SW rate had a significant effect on stone comminution in vivo (Figures 1 and 2). SW treatment at 0.5 Hz was more efficient than at 2 Hz, leaving fewer particles larger than 2 mm (2 mm is clinically relevant, as fragments of this size can be passed from the urinary tract).

Shock arrival time, pressure amplitudes (Figure 3) and the area of positive and negative pressure of the waveform were characteristically responsive to changes in charging potential. However, SW rate had no effect on these parameters. This was surprising since we have observed by b-mode ultrasound and high-speed camera a dramatic, visible increase in bubbles along the SW axis at fast rate. We anticipated that such a buildup of bubbles would act to interfere with propagation of the SW, but direct measurement revealed no change in waveform parameters as a function of rate.

CONCLUSIONS

Our findings demonstrate that slowing the pulse repetition frequency in SWL has a significant positive effect on the efficiency of stone fragmentation in vivo. The implication for clinical SWL is that slower administration of SW’s could improve the efficiency of SWL. Assessment with a membrane hydrophone showed no effect of SW rate on waveform parameters. This suggests that SW rate does not have a profound effect on the lithotripter acoustic field and implies that the mechanism of the rate effect might be localized to the environment of the stone—possibly involving cavitation dynamics at the stone surface.

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REFERENCES

Evidence That Cavitation and Spall Contribute to Stone Failure in an Animal Model of Kidney Stone Fragmentation by Shock Wave Lithotripsy (SWL)

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A variety of in vitro models have been used to investigate stone comminution in SWL and have provided evidence that both cavitation and spall play a role in stone fragmentation. We sought to determine how stones break within the kidney of living animals.

Artificial stones (gypsum cylinders 7.5x6.5mm) were inserted into the kidneys of ~45 kg pigs via percutaneous access. Stones were targeted by fluoroscopy and treated (400SW’s, 20kV) with a Dornier HM3 lithotripter. Kidneys were dissected and stone fragments examined. Many stones revealed damage characteristic of cavitation (erosion) and spall (with the fracture distal to the site of SW impact). The pattern of damage in vivo was similar to that of cohort artificial stones treated under comparable conditions (orientation, stabilization, SW parameters) in vitro. Thus, it appears that artificial stones fragment in vivo by a combination of cavitation and spall damage.

INTRODUCTION

SWL has proven to be an effective therapy for removal of urinary stones. However, SW treatment commonly results in collateral damage to the kidney [1]. The spectre of adverse effects has stimulated research to find ways to enhance stone comminution without causing renal injury. The foundation for the improvement of SWL is to understand how SW’s break stones. Numerous mechanisms have been proposed to explain how SW’s cause stones to fail, and studies with in vitro models have demonstrated that the compressive stress of the focused SW [2] and cavitation caused by the tensile phase of the pressure pulse [3,4] both contribute to stone breakage. Thus, data obtained with in vitro test systems implicate at least two acoustic mechanisms that can be manipulated by controlling the lithotripter waveform. One caveat of work with in vitro models is concern that the in vitro environment may not adequately represent the environment of kidney stones in vivo. That is, how SW’s break stones in vitro may not be how stones are broken in the kidney. To address this concern we characterized the pattern of damage when artificial stones were treated in vitro and compared this to stones implanted in pig kidneys and treated with a clinical lithotripter.

EXPERIMENTAL METHODS

Artificial Stones: Stones (slightly tapered cylinders 7.5 mm x 6.5 mm) were prepared from Ultracal-30 gypsum cement (United States Gypsum, Inc.), cast in 96 well plates, liberated with chloroform and stored in water.

In Vitro Setup: Stones were immobilized with loosely packed water-hydrated cotton gauze and positioned near an acoustically invisible Mylar window in the cap of a plastic centrifuge tube. Thus, SW’s passed through the Mylar and through gauze before striking the stone. Stones were oriented in vitro to approximate the orientation of stones in vivo (i.e. stone long axis perpendicular to, or at ~45° to the SW axis). Stones were exposed to 300 SW’s, 20 kV, using a research electrohydraulic lithotripter patterned after the Dornier HM3 lithotripter [5].

SW Treatment of Stones In Vivo: Stones were implanted in the lower pole calyx of female pigs (~45 kg) via percutaneous access. During a 2 hr recovery period fluoroscopy and diagnostic US were used to rule out abnormal fluid accumulation or air within the collecting system. Stones were stabilized by the walls of the calyx, but were bathed by urine at the flat ends and over portions of the sides of the cylinder. In positioning the animals for lithotripsy the stones were targeted by biplanar fluoroscopy. 400 SW’s were administered at 20 kV.

Analysis of Stone Damage: Following SWL the kidneys were removed and dissected to expose the calyceal system. Stone fragments were collected and dried. Digital images of the fragments were collected and selected stones were analyzed by micro-computed tomography using a Scanco-20 research CT scanner (Scanco, Zurich).
RESULTS AND DISCUSSION

*In vitro* stones were eroded at their proximal surface and they showed fractures (Figure 1). The location of the fractures was dependent on the orientation of the stone relative to the acoustic axis of the lithotripter. That is, when *in vitro* stones were oriented vertically the fracture was transverse (Figure 2, left). When the stone was tilted to approximately 45° the fracture could be longitudinal or transverse (Figure 1, and Figure 2, right).

*In vivo* stones showed a very similar pattern of damage that included erosion on one side and fractures running either along the length of the cylinder or across it (Figures 3 and 4). In experiments with *in vivo* stones it was not possible to be certain of the orientation of the stone to the SW axis. Based upon the position of the animal in the lithotripter we estimate that SW’s entered the stone obliquely (like the 45° stones *in vitro*).

In *in vitro* stones we found that proximal erosion is eliminated when SW’s are administered at overpressure sufficient to preclude cavitation. Fracture of the stones is consistent with failure due to a spall mechanism. Spall occurs when the SW reflects off the distal surface of the stone [2]. The reflected SW reverses phase, is focused within the interior of the stone and the stone fails in tension. The geometry of the stone influences the focus of this reflection and numerical simulations using a finite-difference time-domain code in a two-dimensional geometry can be used to predict the enhancement of the tensile stress and the location of focus [6]. Using this model we estimate that for an incident SW normal to the longitudinal or transverse axis of the stone, spall fracture should occur 2-3 mm inward from the side opposite to SW entry. Our results both *in vivo* and *in vitro* are in agreement with this prediction.

In summary, the pattern of damage to artificial stones implanted in pig kidneys and exposed to SW’s *in vivo* exhibits features (erosion and fractures) consistent with failure by cavitation and by spall.

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