The Acute and Long-Term Adverse Effects of Shock Wave Lithotripsy

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Summary: Shock wave lithotripsy (SWL) has proven to be a highly effective treatment for the removal of kidney stones. Shock waves (SWs) can be used to break most stone types, and because lithotripsy is the only noninvasive treatment for urinary stones, SWL is particularly attractive. On the downside SWL can cause vascular trauma to the kidney and surrounding organs. This acute SW damage can be severe, can lead to scarring with a permanent loss of functional renal volume, and has been linked to potentially serious long-term adverse effects. A recent retrospective study linking lithotripsy to the development of diabetes mellitus has further focused attention on the possibility that SWL may lead to life-altering chronic effects. Thus, it appears that what was once considered to be an entirely safe means to eliminate renal stones can elicit potentially severe unintended consequences. The purpose of this review is to put these findings in perspective. The goal is to explain the factors that influence the severity of SWL injury, update current understanding of the long-term consequences of SW damage, describe the physical mechanisms thought to cause SWL injury, and introduce treatment protocols to improve stone breakage and reduce tissue damage.
Semin Nephrol 28:200-213
Keywords: *Lithotripsy, shock waves, urinary stones, kidney, injury, vascular trauma*

Shock wave lithotripsy (SWL) uses high-energy acoustic pulses (shock waves [SWs]) generated outside the body to break stones within the kidney and ureter. As such, SWL is the only noninvasive method available to remove stones. In the early years after its introduction SWL was considered an option for the treatment of virtually any stone type in any anatomic location. Urologists soon learned, however, that the urinary tract has a limited ability to clear stone fragments and that ureteral obstruction could occur if the mass of stone debris was too high. As such, SWL now is used to treat otherwise uncomplicated solitary stones, or a combined stone burden of less than 2 cm (on KUB), located in the upper urinary tract (renal pelvis or proximal ureter).[1] Not all mineral types respond well to SW. Some calcium oxalate monohydrate stones, brushite stones, and a subtype of cystine can be highly SW-resistant.[2] A noteworthy drawback of SWL is that in many cases stone fragments left behind can serve as foci for the development of new stones.[3] As such, stone-free rates are lower and stone recurrence rates are higher for SWL than with invasive protocols such as ureteroscopy and percutaneous nephrostolithotomy that involve visual localization and extraction of stones.[4] Still, because lithotripsy can be very effective, is noninvasive, and typically is performed on an outpatient basis, SWL is used for the treatment of up to 70% of uncomplicated upper-tract stone cases.[5]

LITHOTRIPTERS AND SHOCK WAVES

Lithotripters differ from one another in the method used to generate SWs (ie, electromagnetic, electrohydraulic spark gap, piezoelectric array), but they are largely the same in that they all produce a very similar acoustic pulse.[6] Lithotripter SWs are characterized by a waveform

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0270-9295/08/$ - see front matter
 doi:10.1016/j.semnephrol.2008.01.003

having a leading positive pressure component of approximately 20 to 110 MPa, followed by a negative pressure phase of approximately −5 to −10 MPa (1 MPa = ~10 atm pressure). The positive phase of the pulse is short lived (~1 μs) and jumps to peak pressure almost instantaneously. It is this portion of the pulse that constitutes the shock of the SW. The focusing mechanism of the lithotripter directs the pulse to an elongated (cigar-shaped) region in space where the patient's stone is positioned for treatment. Lithotripters differ in the dimensions of this focal zone (focal volume) and the acoustic pressure and energy density that occupies this area. Studies on the mechanisms of SW action indicate that the width of the focal zone is an important feature in stone breakage and that stones break better when the focal width exceeds the stone diameter (see later). Most lithotripters have focal widths of approximately 6 to 10 mm, but some are quite narrow (≤4 mm), whereas some are much wider (~16-18 mm). This is an important feature, particularly in regards to recent efforts to improve the efficacy of SWL.

HOW SHOCK WAVES BREAK STONES AND DAMAGE TISSUE

Even though lithotripter SWs are quite powerful, it can take hundreds, even thousands, of pulses to reduce stones to particles fine enough (~2 mm) to be voided through the urinary tract. Breakage tends to be gradual and stones fail by a process of fatigue caused by repetitive stress.[7,8] SWs create microcracks that progressively lengthen and expand until failure occurs. A variety of mechanisms have been proposed to explain how SWs break stones (Table 1), but in simple terms this amounts to two main events: cavitation and direct stress.[6] Cavitation is the formation of bubbles in the urine surrounding the stone, and is driven by the negative pressure phase of the SW. Bubble growth is rapid and collapse can be particularly forceful, generating powerful secondary SWs that radiate from the point of collapse and fluid microjets that produce intense, focused pressures directed at the surface of the stone. Cavitation bubbles form clusters and collapse together to erode the surface of the stone.[9] Cavitation may contribute to all phases of the progressive breakage of stones but appears to be most important in grinding down stone fragments that are too small to be broken by other mechanisms.[10] Thus, cavitation is critical to stone comminution, but also plays a major role in causing tissue damage (see later).

Table 1. Mechanisms of SW Action in SWL

Stone breakage
Shear stress is maximized when the focal zone is larger than the stone, breaks stone into fragments
Cavitation contributes to large-order fragmentation, and breaks fragments into gravel
Tissue injury
Cavitation ruptures blood vessels—typically requires hundreds of SWs to initiate
Shear stress, enhanced at fast SW rate, may break vessels, leading to further cavitation

The large-order fragmentation of stones is caused by internal stresses induced by the compressive, positive pressure phase of the SW. Compressive waves (or acoustic waves) travel through the stone and the surrounding fluid and induce internal stresses within the stone in several ways. Recent studies using numerical modeling have shown that stress waves launch from the surface toward the interior of the stone and are amplified by angles and irregularities at the stone surface.[11] The compressive/acoustic wave also acts to squeeze the stone from the outside, a sort of narrow but intense hoop stress passing along the stone.[12] This inward-directed circumferential stress is critical to fragmentation, and in vitro studies have shown that if the compressive wave is blocked from the stone surface, fragmentation is significantly less efficient.[13] These findings carry an important implication for lithotripsy—that is, stones break better when the focal width of the lithotripter is wider than the stone.

The mechanisms involved in stone breakage help one appreciate the conditions that lead to tissue injury in SWL (Table 1). That is, because stone breakage is a progressive process it subjects the body to repetitive SWs (hundreds to

thousands of SWs). It is also true that some of the same features of the lithotripter acoustic field that contribute to stone breakage also are involved in generating tissue damage—that is, there is a role for cavitation and a possible contribution from shear stress. SWL injury to the kidney is primarily a vascular hemorrhagic lesion.[14,15] There is substantial evidence to show that cavitation plays a role in this damage. For example, conditions that enhance cavitation such as injecting the vasculature with microbubbles, result in increased injury, whereas suppression of the tensile phase of the SW, which is necessary to drive bubble growth, reduces tissue damage.[16-19] Precisely how cavitation breaks vessel walls, particularly in very small diameter vessels, is hard to know. In vitro studies using vessel phantoms suggest that bubble expansion may be involved, and a recent study in which microbubbles were perfused within an ex vivo vascular bed and exposed to ultrasound shows that bubble collapse can occur within small-order vessels and can damage the vascular wall as well.[18,20] Regardless of how cavitation may cause vessels to rupture it is important to note that under normal physiologic conditions the patent vasculature does not readily support cavitation.[16] Although whole blood in vitro or blood pooled within a hematoma in vivo undergoes cavitation readily, cavitation is rare in the circulation. Pig studies using a sensitive technique for passive cavitation detection have shown that it takes many hundreds of SWs to initiate cavitation in the kidney.[21] It seems likely that this is because the conditions necessary to support cavitation require repetitive stress. This opens the question of what conditions must be present for cavitation to occur. One possibility is that cavitation may be dependent on the presence of circulating particulates that act as nuclei for bubble growth. However, what might serve as such a natural cavitation nucleus is unknown.[16,22]

If blood flowing in the circulatory system is such a poor matrix for cavitation, perhaps the substantial cavitation necessary to cause measurable hemorrhage is secondary to some other injury event. That is, perhaps the vessel must fail and blood must pool for cavitation and further damage to be sustained. A recent study modeling the material properties of various tissue compartments within the kidney suggests that shear stress may accumulate within the parenchyma, but only if the rate of SW delivery is faster than the displacement relaxation time of the tissue.[23,24] The model predicts that the degree to which shear induced displacement/deformation occurs will depend on the background structure of the tissue, that is, will be different for different regions of the kidney and be greatest near the tip of the renal papilla. Pig studies show that the renal papilla is particularly sensitive to SWL damage.[19] Thus, the cumulative shear model may be in good agreement with experimental results and may help explain why renal injury is reduced at a slow SW rate (see later).[25]

Table 2. Characteristics of Acute Renal Injury in SWL

Focal hemorrhage in region targeted by focal zone
Rupture of veins, small arteries, and capillaries
Extravasation and pooling of blood
Necrosis of vascular wall
Disruption of podocytes and mesangial cells
Blood within Bowman's space and lumen of renal tubules
Ischemic change in tubular epithelium
Infiltration by inflammatory cells

THE SPECTRUM OF ADVERSE EFFECTS IN SWL: ACUTE RENAL AND EXTRARENAL DAMAGE CAUSED BY SHOCK WAVES

Tissue damage in SWL most often involves trauma localized primarily to the region where the focal zone is targeted (ie, the renal calyceal system), but can include injury to surrounding organs as well (Tables 2 and 3). Understandably, injury to the kidney has received considerably more attention than extrarenal effects. However, reports of damage outside the kidney are noteworthy and may be additional cause for concern. A sampling of such findings (Table 4) includes perforation of the colon, rupture of the hepatic artery, hepatic hematoma, pneumo-

Table 3. Remarkable Renal Injury as a Consequence of SWL

Intraparenchymal and subcapsular hematomas
Rupture of renal pelvis
Proliferative glomerulopathy
Anti–glomerular basement membrane disease
Permanent loss of nephrons
Diffuse fibrosis
Acellular scarring from cortex to inner medulla
Complete papillary necrosis
Irreversible acute renal failure

thorax, urinothorax, rupture of the spleen, acute necrotizing pancreatitis, dissecting abdominal wall abscess, rupture of the abdominal aorta, and iliac vein thrombosis, among others.[26-38]

Virtually all patients who undergo SWL for renal stones show hematuria after receiving about 200 SWs.[1] The occurrence of blood in the urine is so common that it is considered, and rightly so, an incidental finding. The severity of hematuria is rarely a concern, and there was a time when urologists considered a little blood in the urine as a good sign—that the lithotripter was, indeed, targeted on the kidney. For some time it also was thought that hematuria was a consequence of irritation of the urothelium as stone fragments were broken by the SW. However, animal studies soon showed that this was not the case. Detailed morphologic studies in a variety of animals have shown that SWs rupture blood vessels and can damage surrounding renal tubules.[1,14,39,40] The pig is the preferred animal model for SWL injury; treatment results in disruption of a wide range of vessels from glomerular and cortical capillaries and the vasa recta, to the larger arcuate and intralobular vessels.[15,41] When the focal zone is targeted on a lower pole calyx the lesion typically extends from the cortex to medulla, with focal spots of hemorrhage. Details of the lesion in animals killed 4 hours after treatment commonly include torn vessels with platelet aggregation, vacuolization to complete necrosis of the endothelium and vascular smooth muscle, and red blood cells and leukocytes in the interstitial space. Damaged renal corpuscles typically show breaks in Bowman's capsule, blood in the urinary space, and damage to podocytes and mesangial cells. Renal tubules often contain blood cell casts, and the tubular epithelial cells can show injury (vacuolization, sloughed microvilli) characteristic of ischemic change. A typical clinical dose of 2,000 SWs with the Dornier HM3 lithotripter (Dornier Medical Systems, Kennesaw, GA) operated at 24 kV and SWs delivered at 120 SW/min produces a parenchymal lesion measuring approximately 5% to 6% of functional renal volume (FRV).[42]

Perhaps the first indication of the potential for lithotripsy injury in patients came in an early report introducing lithotripsy as an alternative to open surgery.[43] In that study subcapsular hematomas were observed by ultrasonography, but the occurrence was low—less than 1% of patients. Soon, an article by Kaude et al[44] reported a much higher hematoma rate (29%) in patients assessed by magnetic resonance imaging. The Kaude et al[44] report focused attention on the possibility that SWs potentially could cause significant injury. Numerous studies have since reported moderate to severe hemorrhage as a consequence of lithotripsy.[1,14] Case studies describe a variety of severe complications from intraparenchymal, subcapsular, or perirenal bleeding, including irreversible acute renal failure.[45-53] It is interesting to note that severe complications have occurred in the absence of excessive bleeding. One example is a case of irreversible acute renal failure in an individual who developed anti–glomerular basement mem-

Table 4. Extrarenal Injury as a Consequence of SWL

Intra-abdominal bleeding
Abdominal abscess
Splenic rupture and abscess
Liver and pancreatic hematomas
Acute pancreatitis
Pulmonary contusion and hemoptysis
Pneumothorax, urinothorax
Perforation of bowel
Rupture of abdominal aorta, hepatic artery, iliac artery

brane disease, likely as a consequence of glomerular injury during SWL.[54] Values for hematoma rates range from less than 1% to about 20%, and depend on the type of lithotripter used and the radiologic method and timing of the assessment.[48,55,56] Age is an apparent risk factor in hematoma formation, with incidence increasing about 2-fold per decade.[57] Although some hematomas can persist for many months to years, it has been reported that most resolve within weeks and without long-term adverse effects.[58] Thus, SWL has the potential to cause hemorrhage in and around the kidney. In some cases this bleeding is severe and can be catastrophic. It is thought, however, that in most instances renal hematomas resolve spontaneously without apparent long-term adverse effects.

THE POTENTIAL FOR LONG-TERM ADVERSE EFFECTS CAUSED BY SWL

There has yet to be a definitive study performed with experimental animals to fully characterize the manifestations of chronic injury in SWL. It is clear, however, that SWs damage blood vessels and the incidental, or mild to severe, hemorrhage that ensues initiates an inflammatory response and the cascade of events that leads to scar formation.[59] Perhaps the first evidence of lasting SW injury was a study in dogs that showed dose-dependent parenchymal fibrosis at 1 month after treatment.[39] Dose-dependent scar formation also was shown in rabbits in which scar volume increased nearly 10-fold by doubling the dose of SWs from 1,000 to 2,000 pulses.[60] There has yet to be a thorough survey to determine if the kidney expresses a regional susceptibility to scarring, but it has been observed that the inner medulla is prone to damage. Pigs treated with 2,000 SWs can show complete atrophy of renal papillae when the focal zone of the lithotripter is targeted within a lower pole calyx.[1]

It is fair to say that we have a rather incomplete picture of the progression from acute injury to lasting damage, how renal structure and function are affected, and the factors that influence the severity of long-term effects. Still, the work that has been reported indicates that long-term effects are dose dependent, and can involve a permanent loss of functional renal mass. It goes without saying that acute injury precedes lasting effects. However, little is known about the threshold of damage to precipitate a lasting change, where within the kidney acute injury is most likely to lead to chronic changes, whether or not visible change such as scarring truly represents significant damage, and the role that pre-existing risk factors may play in the progression to chronic effects. This is all to say that animal research reported to date, although convincing, that the kidney is susceptible to permanent damage, has only begun to address clinical relevance. Indeed, it is the clinical data that are understandably the most concerning, in particular evidence pointing to the possibility that SWL may cause new-onset hypertension in some patient groups, may exacerbate the progression of stone disease, and may be linked to the development of diabetes mellitus.

New-Onset Hypertension Has Been Linked to SWL

A number of clinical studies have suggested that new-onset hypertension is a potential long-term consequence of SWL.[61,62-67] Among these, one prospective study showed age as a significant risk factor, with an increase in intrarenal resistive index in patients 60 years of age and older.[62] Other studies as well have reported an increase in hypertension among older lithotripsy patients.[66] It appears that transient hypertension can result from formation of subcapsular hematomas.[51] Potential mechanisms for long-term effects have not been determined, although there is a report of mesangial cell proliferation in experimental work with pigs at 1 month post-SWL.[68]

Multiple Lithotripsies May Exacerbate Stone Disease

Kidney stone disease is not a simple problem, and there is ample evidence to show that stone formation involves multiple etiologies.[69] Indeed, it is appropriate to refer to specific stone disease entities such as brushite disease or cystine stone disease in comparison, for example, with idiopathic calcium oxalate (CaOx) stone disease.[70,71] One piece of this story follows the observation

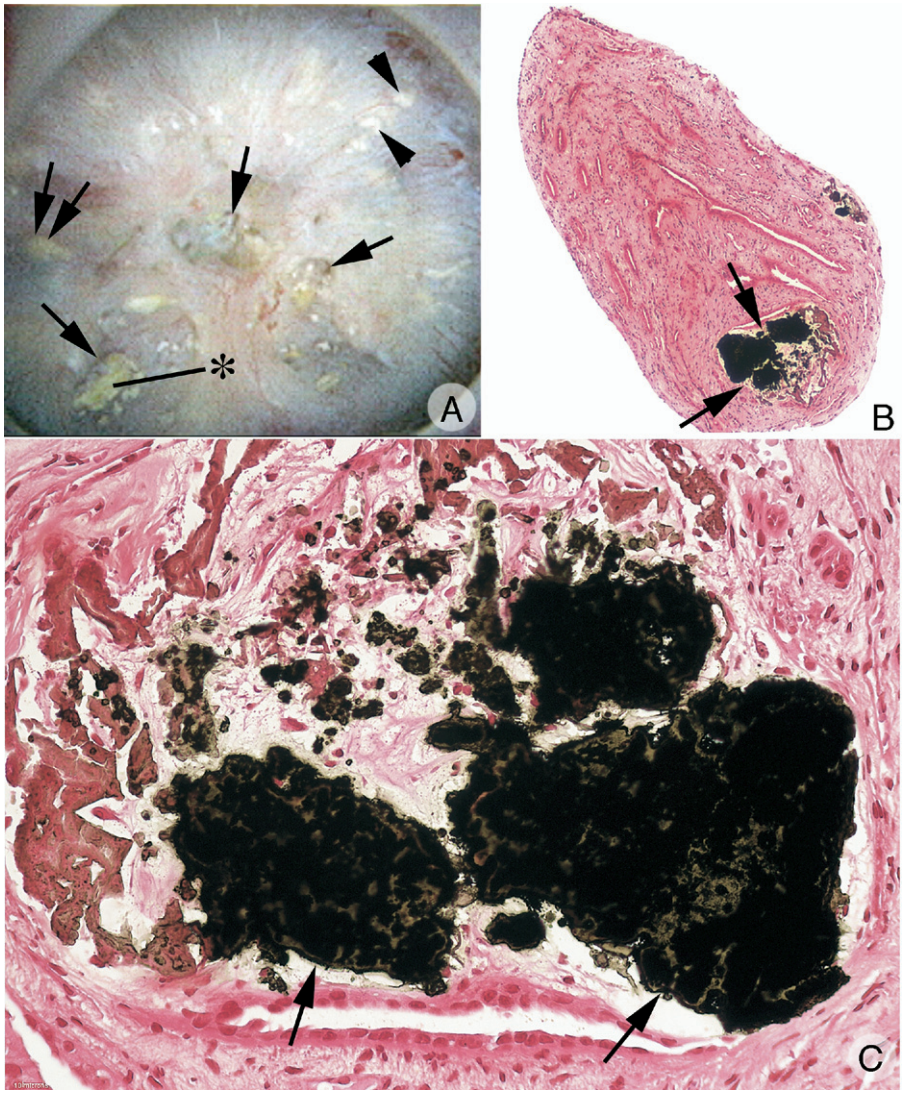

Figure 1. Exacerbation of stone disease may be a consequence of SWL treatment. These images illustrate the morphologic features of the renal papilla from a patient with brushite kidney stone disease. This patient received 5 SWL sessions before the onset of brushite stones. (A) Endoscopic view of a renal papilla showing 3 dilated openings (arrows) to the ducts of Bellini, one of which has a plug of apatite protruding from its lumen (asterisk). In addition, sites of Randall's plaque appear as irregular whitish areas (arrowheads) next to sites of yellow plaque (double arrows) representing crystalline deposits in the lumen of inner medullary collecting ducts. (B) Tissue section of papillary biopsy specimen stained by the Yasue method for calcium showing blockage of a duct of Bellini (arrows) with a surrounding cuff of interstitial fibrosis. (C) At higher magnification, sites of Yasue-positive material (arrows) are seen embedded within fibrotic/atrophic tissue.

that over the past 3 decades there has been an increase in the occurrence of calcium phosphate (CaP) stones within the population.[72] A potential explanation for this shift has been difficult to find. That is, until it was observed recently that a correlation exists between the percentage of CaP in stones and the number of lithotripsy sessions in the cohort.[73] The data showed that CaP stone formers underwent a greater number of lithotripsies than did CaOx stone formers, and patients with brushite stones underwent SWL more than either of these groups. This may suggest the possibility that SWL is linked to a transition from CaOx disease to brushite disease, a change toward a more complicated pathology.[70] The implication is that multiple lithotripsies for the treatment of CaOx stones may cause progressive injury in the renal

papilla that alters the normal physiology of the collecting ducts, and fuels the formation of intraluminal crystalline deposits of apatite—a process that typically involves tubular atrophy, even papillary necrosis. Thus, multiple lithotripsies could be driving the formation of brushite, a mineral type that does not respond well to SWs, and often is considered a contraindication for SWL (Fig. 1).

Diabetes Mellitus May be Linked to Multiple Lithotripsies

It is well documented that SWL for treatment of stones within the kidney can cause extrarenal soft-tissue damage (see previously).[14,37,38] The occurrence of injury to the bowel, liver, spleen, or some other organ does not necessarily mean that the lithotripter was targeted incorrectly. Although a lithotripter typically is characterized by the temporal and spatial distribution of acoustic energy within its focal zone, it should be appreciated that this region does not define the limits of high acoustic pressures generated by the SW. The focal zone is the area that contains the highest acoustic pressure and highest energy density, but SW pressures of both the compressive and tensile phases of the pulse can be relatively high outside this volume. The pressure threshold for initiation of cavitation is on the order of only about -1 to -2 MPa, and such pressures can be measured many centimeters off the acoustic axis.[6] This is all to say that it is reasonable to expect that organs other than the kidney will be subjected to stresses sufficient to cause injury during SWL. This explains why it is not easy to dismiss on mechanistic grounds the idea that the pancreas could be damaged during lithotripsy, and that this injury might lead to long-term effects such as diabetes.

A retrospective 19-year follow-up study from the Mayo Clinic suggested that patients who underwent SWL for the treatment of kidney stones in 1985 were at increased risk of developing diabetes mellitus compared with controls.[61] Occurrence of diabetes in these patients was related to the total number of SWs and the power level of the lithotripter. The investigators were duly cautious in their approach, and in this and a subsequent report noted a number of limitations to the study.[74] For example, the data for the SWL group were collected by self-report questionnaire, whereas the control group was examined via chart review. Based on stone size, the stone disease of the SWL group was more severe than in the control group. In addition, family history for diabetes was not determined for either group. The report stimulated considerable discussion within the urology community.[75,76] Similar to the data suggesting that multiple lithotripsies may be linked to an exacerbation of stone disease (see previously), these findings are new and have as yet to be validated independently. Still, similar to new-onset hypertension or a transformation of stone disease, the possibility of diabetes as an outcome of SWL represents a potential side effect that ought to be cause for concern, and clearly deserves further investigation.

FACTORS THAT AFFECT THE SEVERITY OF SWL INJURY

Animal studies have shown that renal injury in SWL is dependent on the number of SWs delivered, the power setting of the lithotripter, and the rate of SW delivery.[26,77-83] The idea that SW dose is important seems intuitive and it makes sense that steps should be taken whenever possible to reduce SW exposure. The suggestion that some long-term effects could be linked to repetitive injury from multiple lithotripsies also seems to be a reasonable possibility. The effects of SW rate are a lot less obvious. Early in the evolution of SWL, lithotripters were developed that could fire at extremely fast rates, with the idea of shortening treatment time, and studies were conducted to assess tissue effects. Rates of 900 SW/min and higher were tested and were found to create significantly more damage than the conventional rate of 60 to 120 SW/min.[81,82] Cavitation and the potential for cumulative shear both are enhanced as the SW rate is increased, so both mechanisms may well be involved in injury at extremely fast SW rates.[6,22-24] Current practice is to treat patients at 60 to 120 SW/min and the vast majority of the literature on SWL adverse effects is for treatment in this range. Recent studies now have shown that slowing the SW rate to approximately 30 SW/min has a dramatic protective

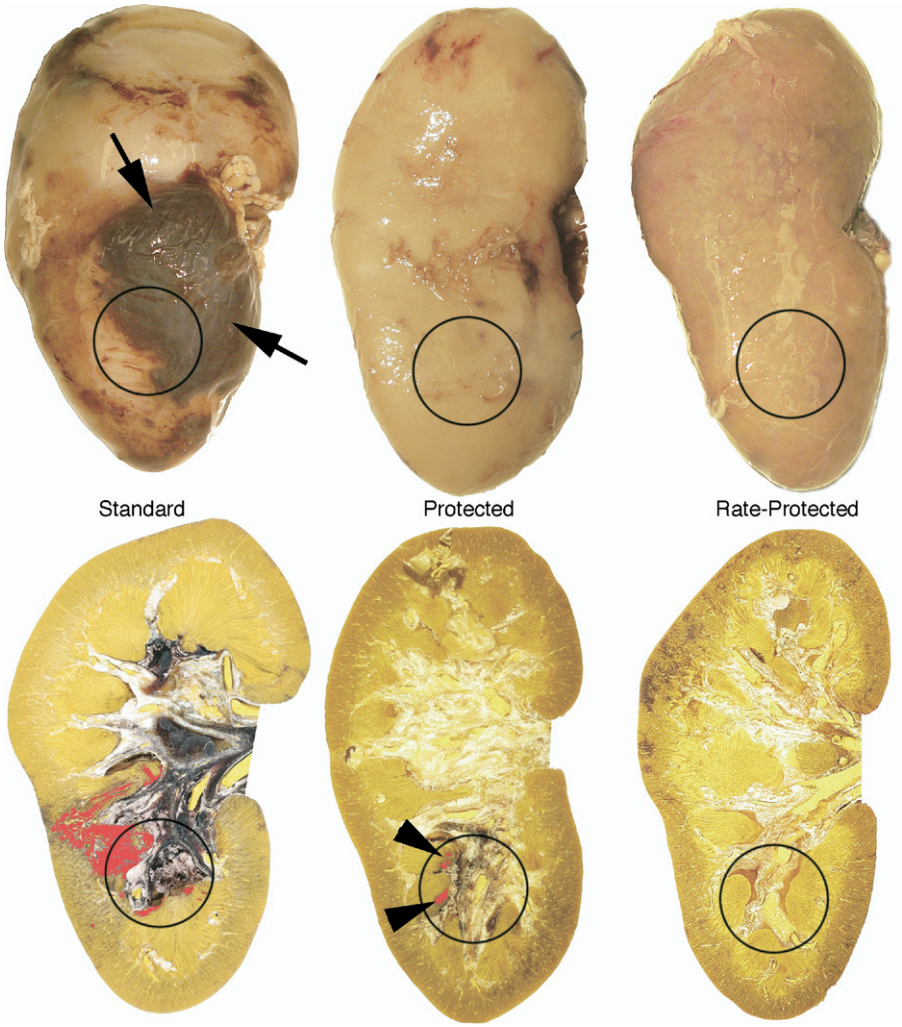

Figure 2. Demonstration that proper treatment strategies can protect against kidney injury in SWL. The top row shows the exterior kidney surface and the bottom row shows the macroscopic images of sections through 3 pig kidneys after different treatment protocols using the Dornier HM3 lithotripter (24 kV). Circles indicate the approximate location of the focal zone targeted to the lower pole. Tissue sections depict morphometric segmentation of regions showing parenchymal hemorrhage (digitally colored red). (Left) Standard treatment protocol in which the pig received 2,000 SWs at 120 SW/min. The kidneys typically developed subcapsular hematomas (arrows). The hemorrhagic lesion in this kidney, determined from serial sections, measured approximately 5% FRV. (Middle) Protective effect of voltage ramping at a standard rate. This pig received a priming dose of 500 SWs at low energy (12 kV) followed by 2,000 SWs (24 kV) all at 120 SW/min. The lesion, limited to the tips of renal papillae (arrowhead), is reduced dramatically (~.3% FRV) compared with the injury seen with the standard protocol. (Right) The protective effect of slow SW rate. This animal was treated with 2,000 SWs delivered at 30 SW/min. No lesion is visible in this section. Injury at a slow rate as determined from serial sections measured less than 0.1% FRV.

effect, and a slow rate may be an important strategy for the future (see later).

A number of factors have been identified that may place patients at increased risk of injury in SWL. Because SW injury is dominated by vascular trauma it is not surprising that patients with clotting disorders experience greater damage.[84] A bleeding diathesis can significantly lower the threshold for severe injury, and there is a report of uncontrolled renal hemorrhage in a patient who received only 250 SWs.[85] History of a bleeding disorder is, indeed, considered a contraindication for SWL, as is a current course of anticoagulants or even aspirin.[1,52] Age has been shown to be a factor in the occurrence of hematomas and in the development of new-onset

hypertension after SWL.[57,62,66] Kidney size also influences the degree of injury that occurs. The kidneys of juvenile pigs showed more extensive lesions than developed in young adult animals treated with the same dose, and although lithotripsy is considered an option for the treatment of children, there is evidence of delayed kidney growth in pediatric patients treated by SWL.[1,86,87] Little is known about the effect of renal disease on the susceptibility of the kidney to SW injury, although it has been shown that tissue damage is accentuated dramatically in a pig model of pyelonephritis.[88]

THE TYPICAL TREATMENT PROTOCOL AND NEW STRATEGIES THAT REDUCE SWL INJURY

How SWs are delivered matters. That is, the settings used and the sequence of SW delivery affect the efficiency of stone breakage and the severity of injury that can occur during treatment. Although guidelines have been developed to improve treatment outcomes, there is no widely accepted protocol for best practice that takes into account current understanding of the mechanisms of SW action. During treatment the urologist has control over the power setting of the lithotripter, the number of SWs, and the firing rate. Most urologists are well aware that injury is a potential outcome in SWL and do what they can to minimize SW exposure. However, this can be difficult to do. Most patients likely receive more SWs than are needed to break their stones because lithotripsy imaging systems (fluoroscopy or ultrasound) do not allow one to see when the stone is broken to completion. Because stones are highly variable in their fragility to SWs it is difficult to estimate the dose based on stone burden alone.[2] Progress has been made in using laboratory computerized tomography to predict fragility, but this must be refined further before it is useful at the clinical level.[89] Because of this, patients often may be treated with the maximum number of SWs allowable for the lithotripter at hand (~2,500-4,500 SWs).

SWL injury also is dependent on power level but here too there is room for excess.[79] Most lithotripters are engineered to deliver a broad range of output, but the top end is typically much higher than is needed to break stones. A recent study in pigs using the Dornier HM3 lithotripter showed that delivering SW with a step-wise increase in power setting acts to reduce lesion size[42] (Fig. 2). Injury was reduced significantly when treatment was initiated at 12 kV (first 100 SWs) followed by the remainder of the dose (2,400 SWs) at 24 kV, compared with all SWs at the high setting. This was the first indication that SWs could be used as the foundation for a strategy to protect the kidney from damage during further treatment (Table 5). Treatment with a priming dose of low-energy SWs induces transient vasoconstriction in both the treated and the contralateral kidneys.[77] How vasoconstriction may contribute to protection is unclear, but this finding is an indication that the kidney is very responsive to focal stress.

Table 5. Treatment Strategies Shown to Reduce Renal Injury in Experimental Animals

Delivering fewer SWs
Reducing the power setting of the lithotripter
Pretreatment with SWs at low energy significantly reduces lesion size
Treatment at slow SW rate (30 SW/min) virtually eliminates renal vascular injury

SW rate is the basis of an even more effective treatment strategy, one that both protects against injury and also improves stone breakage. Most patients typically are treated at a rate of 120 SW/min. A number of clinical studies have reported, however, that slowing the SW rate to 60 to 90 SW/min actually improves the success rate.[90-94] The acoustic mechanism for this effect involves cavitation. When stones are treated at a fast SW rate the surrounding fluid is charged with an increased number of minute microbubbles that persist between SWs and serve to seed cavitation with the next pulse.[95] Thus, cavitation is enhanced at a fast rate compared with a slow rate. Cavitation bubble growth occurs at the expense of negative pressure from the tensile phase of the SW, such that at a fast rate the tensile phase of the pulse is

depleted sufficiently to alter bubble cluster activity involved in stone breakage.[96,97]

Reports of improved stone breakage at slow SW rates prompted an animal study to determine if slowing the SW rate was safe. That is, clearly clinical stone breakage outcomes are improved by slowing the SW rate, but if this modification in procedure were to increase tissue damage the overall benefit would be lost. Pigs were treated with 2,000 SWs (24 kV) at either 120 or 30 SW/min and then processed for morphometric quantitation of the parenchymal lesion. The result was surprising.[25] As expected from experience with earlier studies, the animals treated at the faster rate showed a parenchymal lesion occupying approximately 5% FRV. The pigs treated at the slower rate, however, had a vastly reduced lesion (<.1% FRV) limited to renal papillae in the region of the focal zone of the lithotripter (Fig. 2). Thus, slowing the rate of SW administration significantly reduced tissue injury. A similar finding was observed recently in a study to assess the renal injury produced by a novel electromagnetic lithotripter (XX-ES, XiXin-Eisenmenger, XiXin Medical Instruments, Suzhou, China) with a very broad focal zone (~18 mm).[83] In that study pigs were treated at the same settings (1,500 SWs, ~17 MPa at 9.3 kV, 27 SW/min) used to treat patients with the XX-ES, and compared with animals treated with the same number of SWs at comparable settings (~32 MPa at 18 kV, 30 SW/min) with the Dornier HM3 lithotripter.[98] Both groups showed extremely low injury rates. The HM3 group showed a barely detectable lesion (<.1% FRV), whereas in the XX-ES group the lesion was too slight to quantify. Both of these experiments showed that vascular damage in the kidney can be virtually eliminated by slowing the SW firing rate. However, this protection was afforded by treating at a SW rate that is much slower than is typically used clinically. Further study will be needed to determine if intermediate rates (60-90 SW/min) also are protective.

SUMMARY: SHOCK WAVE INJURY AND THE PROGNOSIS FOR LITHOTRIPSY

It is clear that lithotripter SWs have the potential to cause tissue damage and that acute injury can lead to chronic adverse effects. Still, lithotripsy is the only noninvasive means to remove stones and this makes it particularly valuable. Injury, such as stone breakage, is progressive and it typically takes hundreds of SWs to cause significant tissue damage. There is a threshold for tissue injury that depends on multiple factors including the type of lithotripter being used, but little has been done to define the limits of treatment. Patients typically receive more SWs than should be necessary to eliminate their stones because there is no good method to determine when breakage is complete. The severity of acute injury and the potential for progression to long-term effects depends on the SW dose and whether multiple treatment sessions were involved, but also on pre-existing risk factors. Although severe acute injury can occur it is not known if the damage from a single, typical treatment session can lead to long-term effects.

Research suggests that lithotripsy may be linked to several potentially serious chronic adverse effects including new-onset hypertension, the exacerbation of stone disease, and the development of diabetes mellitus. The data for hypertension are the most compelling, whereas the data for transformation of stone disease are new and not yet validated, as is the finding that SWL may be linked to diabetes.

Thus, there is no question that there is a risk of injury with SWL. However, new treatment protocols have been developed recently that significantly improve stone breakage and dramatically reduce acute tissue damage. In particular, the data showing that treating with a progressive increase in SW energy is protective, and that slowing the rate of SW administration can virtually eliminate acute tissue injury, indicates that SWL can be performed safely. As protective treatment protocols begin to be adopted it is hoped that long-term adverse effects also will be reduced, and perhaps eliminated entirely.

REFERENCES

1. Lingeman JE, Matlaga B, Evan AP. Surgical management of urinary lithiasis. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ, editors. Campbell's urology. Philadelphia: WB Saunders Company; 2006. p. 1431-507.

2. Williams JC Jr, Saw KC, Paterson RF, Hatt EK, McAteer JA, Lingeman JE. Variability of renal stone fragility in shock wave lithotripsy. Urology. 2003;61: 1092-7.
3. Carr LK, Honey JD'A, Jewett MAS, Ibanez D, Ryan M, Bombardier C. New stone formation: a comparison of extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy. J Urol. 1996;155:1565-7.
4. Fine JK, Pak CYC, Preminger GM. Effect of medical management and residual fragments on recurrent stone formation following shock wave lithotripsy. J Urol. 1995;153:27-33.
5. Kerbl K, Rehman J, Landman J, Lee D, Sundaram C, Clayman RV. Current management of urolithiasis: progress or regress? J Endourol. 2002;16:281-8.
6. Cleveland RO, McAteer JA. The physics of shock wave lithotripsy. In: Smith AD, Badlani GH, Bagley DH, Clayman RV, Docimo SG, Jordan GH, et al, editors. Smith's textbook on endourology. Hamilton, Ontario, Canada: BC Decker, Inc.; 2007. p. 317-32.
7. Sturtevant B. Shock wave physics of lithotripters. In: Smith AD, editor. Smith's textbook of endourology. St. Louis: Quality Medical Publishing, Inc.; 1996. p. 529-52.
8. Lokhandwalla M, Sturtevant B. Fracture mechanics model of stone comminution in ESWL and implications for tissue damage. Phys Med Biol. 2000;45:1923-40.
9. Pishchalnikov YA, Sapozhnikov OA, Bailey MR, Williams JC Jr, Cleveland RO, Colonius T, et al. Cavitation bubble cluster activity in the breakage of kidney stones by lithotripter shock waves. J Endourol. 2003; 17:435-46.
10. Zhu S, Cocks FH, Preminger GM, Zhong P. The role of stress waves and cavitation in stone comminution in shock wave lithotripsy. Ultrasound Med Biol. 2002; 28:661-71.
11. Cleveland RO, Sapozhnikov OA. Modeling elastic wave propagation in kidney stones with application to shock wave lithotripsy. J Acoust Soc Am. 2005; 118:2667-76.
12. Eisenmenger W. The mechanisms of stone fragmentation in ESWL. Ultrasound Med Biol. 2001;27:683-93.
13. Sapozhnikov OA, Maxwell AD, MacConaghy B, Bailey MR. A mechanistic analysis of stone fracture in lithotripsy. J Acoust Soc Am. 2007;121:1190-202.
14. Evan AP, McAteer JA. Q-effects of shock wave lithotripsy. In: Coe FL, Favus MJ, Pak CYC, Parks JH, Preminger GM, editors. Kidney stones: medical and surgical management. Philadelphia: Lippincott-Raven; 1996. p. 549-70.
15. Shao Y, Connors BA, Evan AP, Willis LR, Lifshitz DA, Lingeman JE. Morphological changes induced in the pig kidney by extracorporeal shock wave lithotripsy: nephron injury. Anat Rec. 2003;275A:979-89.
16. Carstensen EL, Gracewski S, Dalecki D. The search for cavitation in vivo. Ultrasound Med Biol. 2000;26: 1377-85.
17. Matlaga BR, McAteer JA, Connors BA, Handa RK, Evan AP, Williams JC, et al. The potential for cavitation-mediated tissue damage in shock wave lithotripsy. J Endourol. 2008;22:121-6.
18. Zhong P, Zhou Y, Zhu S. Dynamics of bubble oscillation in constrained media and mechanisms of vessel rupture in SWL. Ultrasound Med Biol. 2001;27:119-34.
19. Evan AP, Willis LR, McAteer JA, Bailey MR, Connors BA, Shao Y, et al. Kidney damage and renal functional changes are minimized by waveform control that suppresses cavitation in SWL. J Urol. 2002;168:1556-62.
20. Caskey CF, Steiger SM, Qin S, Dayton PA, Ferrara KW. Direct observations of ultrasound microbubble contrast agent interaction with microvessel wall. J Acoust Soc Am. 2007;122:1191-200.
21. Bailey MR, Pishchalnikov YA, Sapozhnikov OA, Cleveland RO, McAteer JA, Miller NA, et al. Cavitation detection during shock wave lithotripsy. Ultrasound Med Biol. 2005;31:1245-56.
22. Miller DL. Overview of experimental studies of biological effects of medical ultrasound caused by gas body activation and inertial cavitation. Prog Biophys Mol Biol. 2007;93:314-30.
23. Freund JB. A possible cumulative shear mechanism for tissue damage initiation in SWL. In: Evan AP, Lingeman JE, Williams JC, editors. Renal Stone disease: proceedings of the First International Urolithiasis Research Symposium. Melville, NY: American Institute of Physics; 2007. p. 356-9.
24. Freund JB, Colonius T, Evan AP. A cumulative shear mechanism for tissue damage initiation in shock-wave lithotripsy. Ultrasound Med Biol. 2007;33:1495-1503.
25. Evan AP, McAteer JA, Connors BA, Blomgren PM, Lingeman JE. Renal injury in SWL is significantly reduced by slowing the rate of shock wave delivery. BJU Int. 2007;100:624-7.
26. Castillon I, Frieyro O, Gonzalez-Enguita C, Vela-Navarrete R. Colonic perforation after extracorporeal shock wave lithotripsy. BJU Int. 1999;83:720-1.
27. Beatrice J, Strebel RT, Pfammatter T, Rohweder JH, Sulser T. Life-threatening complication after right renal extracorporeal shock wave lithotripsy: large hepatic haematoma requiring embolisation of the right hepatic artery. Eur Urol. 2007;52:909-11.
28. Fugita OE, Trigo-Rocha F, Mitre AI, Arap S. Splenic rupture and abscess after extracorporeal shock wave lithotripsy. Urology. 1998;52:322-3.
29. Karakayali F, Sevmi S, Ayvaz I, Tekin I, Boyvat F, Moray G. Acute necrotizing pancreatitis as a rare complication of extracorporeal shock wave lithotripsy. Int J Urol. 2006;13:613-5.
30. Hassan I, Zietlow SP. Acute pancreatitis after extracorporeal shock wave lithotripsy for a renal calculus. Urology. 2002;60:1111iii-v.
31. Oguzulgen IK, Oguzulgen AI, Sinik Z, Kokturk O, Ekim N, Karaoglan U. An unusual cause of urinothorax. Respiration. 2002;69:273-4.
32. Unal B, Kara S, Bilgili Y, Basar H, Yilmaz E, Batislam E. Giant abdominal wall abscess dissecting into thorax as a complication of ESWL. Urology. 2005;65:389e16-8.
33. Neri E, Capannini G, Diciolla F, Carone E, Tripodi A,

Tucci E, et al. Localized dissection and delayed rupture of the abdominal aorta after extracorporeal shock wave lithotripsy. J Vasc Surg. 2000;31:1052-5.
34. Tiede JM, Lumpkin EN, Wass CT, Long TR. Hemoptysis following extracorporeal shock wave lithotripsy: a case of lithotripsy-induced pulmonary contusion in a pediatric patient. J Clin Anesth. 2003;15:530-3.
35. Meyer JJ, Cass AS. Subcapsular hematoma of the liver after renal extracorporeal shock wave lithotripsy. J Urol. 1995;154:516-7.
36. Malhotra V, Rosen RJ, Slepian RL. Life-threatening hypoxemia after lithotripsy in an adult due to shock-wave-induced pulmonary contusion. Anesthesiology. 1991;75:529-31.
37. Gayer G, Hertz M, Stav K, Zissin R. Minimally invasive management of urolithiasis. Semin Ultrasound CT MR. 2007;27:139-51.
38. Skolarikos A, Alivizatos G, de la Rosette J. Extracorporeal shock wave lithotripsy 25 years later: complications and their prevention. Eur Urol. 2006;50: 981-90.
39. Newman R, Hackett R, Senior D, Brock K, Feldman J, Sosnowski J, et al. Pathological effects of ESWL on canine renal tissue. Urology. 1987;29:194-200.
40. Karlsen SJ, Berg KJ. Acute changes in renal function following extracorporeal shock wave lithotripsy in patients with a solitary functioning kidney. J Urol. 1991;145:253-6.
41. Evan AP, Willis LR, Connors B, Reed G, McAteer JA, Lingeman JE. Shock wave lithotripsy-induced renal injury. Am J Kidney Dis. 1991;17:445-50.
42. Willis LR, Evan AP, Connors BA, Handa RK, Blomgren PM, Lingeman JE. Prevention of lithotripsy-induced renal injury by pretreating kidneys with low-energy shock waves. J Am Soc Nephrol. 2006;17:663-73.
43. Chaussy C, Schmiedt E. Extracorporeal shock wave lithotripsy (ESWL) for kidney stones: an alternative to surgery? Urol Radiol. 1984;6:80-7.
44. Kaude JV, Williams CM, Millner MR, Scott KN, Finlayson B. Renal morphology and function immediately after extracorporeal shock-wave lithotripsy. AJR Am J Roentgenol. 1985;145:305-13.
45. Treglia A, Moscoloni M. Irreversible acute renal failure after extracorporeal shock wave lithotripsy. J Nephrol. 1999;12:190-2.
46. Baskin LS, Stoller ML. Severe haemorrhage after extracorporeal shock wave lithotripsy: radiological evaluation. Br J Urol. 1992;69:214-5.
47. Maziak DE, Ralph-Edwards A, Deitel M, Wait J, Watt HJ, Marcuzzi A. Massive perirenal and intra-abdominal bleeding after shock-wave lithotripsy: case report. Can J Surg. 1994;37:329-32.
48. Rubin JI, Arger PH, Pollack HM, Banner MP, Coleman BG, Mintz MC, et al. Kidney changes after extracorporeal shock wave lithotripsy: CT evaluation. Radiology. 1987;162:21-4.
49. Matin SF, Hsu THS, Klein EA, Streem SB. Acute renal failure due to subcapsular renal hematoma in a solitary kidney: improvement after decompression. J Urol. 2002;168:2526-7.
50. Tuteja AK, Pulliam JP, Lehman TH, Elzinga LW. Anuric renal failure from massive bilateral renal hematoma following extracorporeal shock wave lithotripsy. Urology. 1997;50:606-8.
51. Lemann J Jr, Taylor AJ, Collier BD, Lipchik EO. Kidney hematoma due to extracorporeal shock wave lithotripsy causing transient renin mediated hypertension. J Urol. 1991;145:1238-41.
52. Ruiz H, Saltman B. Aspirin-induced bilateral renal hemorrhage after extracorporeal shock wave lithotripsy therapy: implications and conclusions. J Urol. 1990;143:791-2.
53. Knapp PM, Kulb TB, Lingeman JE, Newman DM, Mertz JHO, Mosbaugh PG, et al. Extracorporeal shock-wave lithotripsy-induced perirenal hematomas. J Urol. 1988;139:700-3.
54. Sellin L, Quack I, Weiner SM, Waldherr R, Henning B, Hofebauer S, et al. Nephrolithiasis and hematuria—sometimes a stony road to diagnosis. Clin Nephrol. 2005;64:151-4.
55. Baumgartner B, Dickey KW, Ambrose SS, Walton KN, Nelson RC, Bernardino ME. Kidney changes after extracorporeal shock wave lithotripsy: appearance on MR imaging. Radiology. 1987;163:531-4.
56. Evan AP, Willis LR. Extracorporeal shock wave lithotripsy: complications. In: Smith AD, Badlani GH, Bagley DH, Clayman RV, Docimo SG, Jordan GH, et al, editors. Smith's textbook on endourology. Hamilton, Ontario, Canada: BC Decker, Inc.; 2007. p. 353-65.
57. Dhar NB, Thornton J, Karafa MT, Streem SB. A multivariate analysis of risk factors associated with subcapsular hematoma formation following electromagnetic shock wave lithotripsy. J Urol. 2004;172:2271-4.
58. Krishnamurthi V, Streem SB. Long-term radiographic and functional outcome of extracorporeal shock wave lithotripsy induced perirenal hematomas. J Urol. 1995; 154:1673-5.
59. Evan AP, Willis LR, Lingeman JE, McAteer JA. Renal trauma and the risk of long-term complications in shock wave lithotripsy. Nephron. 1998;78:1-8.
60. Morris JA, Husmann DA, Wilson WT, Preminger GM. Temporal effects of shock wave lithotripsy. J Urol. 1991;145:881-3.
61. Krambeck AE, Gettman MT, Rohlinger AL, Lohse CM, Patterson DE, Segura JW. Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup. J Urol. 2006;175:1742-7.
62. Janetschek G, Frauscher F, Knapp R, Hofle G, Peschel R, Bartsch G. New onset hypertension after extracorporeal shock wave lithotripsy: age related incidence and prediction by intrarenal resistive index. J Urol. 1997;158:346-51.
63. Knapp R, Frauscher F, Helweg G, Judmaier W, Strasser H, Bartsch G, et al. Blood pressure changes after extracorporeal shock wave nephrolithotripsy:

prediction by intrarenal resistive index. Eur Radiol. 1996;6:665-9.
64. Williams CM, Kaude JV, Newman RC, Peterson JC, Thomas WC. Extracorporeal shock-wave lithotripsy: long-term complications. AJR Am J Roentgenol. 1988; 150:311-5.
65. Frauscher F, Hofle G, Janetschek G. A randomized controlled trial to assess the incidence of new onset hypertension in patients after shock wave lithotripsy for asymptomatic renal calculi [editorial]. J Urol. 1999;162:806.
66. Knapp R, Frauscher F, Helweg G, zur Nedden D, Strasser H, Janetschek G, et al. Age-related changes in resistive index following extracorporeal shock wave lithotripsy. J Urol. 1995;154:955-8.
67. Bataille P, Cardon G, Bouzernidji M, El Esper N, Pruna A, Ghazali A, et al. Renal and hypertensive complications of extracorporeal shock wave lithotripsy: who is at risk? Urol Int. 1999;62:195-200.
68. Banner B, Ziiesmer D, Collins LA. Proliferative glomerulopathy following shock wave lithotripsy in the pig. J Urol. 1991;146:1425-8.
69. Evan AP, Coe FL, Lingeman JE, Worcester E. Insights on the pathology of kidney stone formation. Urol Res. 2005;33:383-9.
70. Evan AP, Lingeman JE, Coe FL, Shao Y, Parks JH, Bledsoe SB, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. Kidney Int. 2005;67:576-91.
71. Evan AP, Coe FL, Lingeman JE, Shao Y, Matlaga BR, Kim SC, et al. Renal crystal deposits and histopathology in patients with cystine stones. Kidney Int. 2006; 69:2227-35.
72. Mandel N, Mandel I, Fryjoff K, Rejniak T, Mandel G. Conversion of calcium oxalate to calcium phosphate with recurrent stone episodes. J Urol. 2003;169: 2026-9.
73. Parks JH, Worcester E, Coe FC, Evan AP, Lingeman JE. Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. Kidney Int. 2004; 66:777-85.
74. Krambeck AE, Rohlinger AL, Lohse CM, Patterson DE, Gettman MT. Shock wave lithotripsy: effects on the pancreas and recurrent stone disease. In: Evan AP, Lingeman JE, Williams JC, editors. Renal stone disease: proceedings of the First International Urolithiasis Research Symposium. Melville, NY: American Institute of Physics; 2007. p. 302-10.
75. Tiselius HG. Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup [editorial]. Eur Urol. 2006;50:612-9.
76. Whitfield HN. Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup [editorial]. Eur Urol. 2006;51:281.
77. Willis LR, Evan AP, Connors BA, Shao Y, Blomgren PM, Pratt JH, et al. Shockwave lithotripsy: dose-related effects on renal structure, hemodynamics, and tubular function. J Endourol. 2005;19:90-101.
78. Connors BA, Evan AP, Blomgren PM, Willis LR, Handa RK, Lifshitz DA, et al. Reducing shock number dramatically decreases lesion size in a juvenile kidney model. J Endourol. 2006;20:607-11.
79. Connors BA, Evan AP, Willis LR, Blomgren PM, Lingeman JE, Fineberg NS. The effect of discharge voltage on renal injury and impairment caused by lithotripsy in the pig. J Am Soc Nephrol. 2000;11:310-8.
80. Delius M, Enders G, Xuan ZR, Liebich HG, Brendel W. Biological effects of shock waves: kidney damage by shock waves in dogs— dose dependence. Ultrasound Med Biol. 1988;14:117-22.
81. Delius M, Enders G, Xuan ZR, Liebich HG, Brendel W. Biological effects of shock waves: kidney haemorrhage by shock waves in dogs—administration rate dependence. Ultrasound Med Biol. 1988;14:689-94.
82. Delius M, Mueller W, Goetz A, Liebich HG, Brendel W. Biological effects of shock waves: kidney hemorrhage in dogs at a fast shock wave administration rate of fifteen Hertz. J Lithotripsy Stone Dis. 1990;2:103-10.
83. Evan AP, McAteer JA, Connors BA, Pishchalnikov YA, Handa RK, Blomgren P, et al. Independent assessment of a wide-focus, low-pressure electromagnetic lithotripter: absence of renal bioeffects in the pig. BJU Int. 2007;101:382-8.
84. Newman LH, Saltzman B. Identifying risk factors in development of clinically significant post-shock-wave lithotripsy subcapsular hematomas. Urology. 1991;38:35-8.
85. Donahue LA, Linke CA, Rowe JM. Renal loss following extracorporeal shock wave lithotripsy. J Urol. 1989;142:809-11.
86. Willis LR, Evan AP, Connors BA, Blomgren P, Fineberg NS, Lingeman JE. Relationship between kidney size, renal injury, and renal impairment induced by shock wave lithotripsy. J Am Soc Nephrol. 1999;10:1753-62.
87. Lifshitz DA, Lingeman JE, Zafar FS, Hollensbe DW, Nyhuis AW, Evan AP. Alterations in predicted growth rates of pediatric kidneys treated with extracorporeal shockwave lithotripsy. J Endourol. 1998;12:469-75.
88. Evan AP, Connors BA, Pennington DJ, Blomgren PM, Lingeman JE, Fineberg NS, et al. Renal disease potentiates the injury caused by SWL. J Endourol. 1999;13: 619-28.
89. Zarse CA, Hameed TA, Jackson ME, Pishchalnikov YA, Lingeman JE, McAteer JA, et al. CT visible internal stone structure— but not Hounsfield unit value— of calcium oxalate monohydrate (COM) calculi predicts lithotripsy fragility in vitro. Urol Res. 2007;35:201-6.
90. Pace KT, Ghiculete D, Harju M, Honey RJD'A. Shock wave lithotripsy at 60 or 120 shocks per minute: a randomized, double-blind trial. J Urol. 2005;174:595-9.
91. Yilmaz E, Batislam E, Basar M, Tuglu D, Mert C, Basar H. Optimal frequency in extracorporeal shock wave lithotripsy: prospective randomized study. Urology. 2005; 66:1160-4.
92. Madbouly K, El-Tiraifi AM, Seida M, El-Faqih SR, Atassi R, Talic RF. Slow versus fast shock wave lithotripsy

rate for urolithiasis: a prospective randomized study. J Urol. 2005;173:127-30.
93. Chacko J, Moore M, Sankey N, Chandhoke PS. Does a slower treatment rate impact the efficacy of extracorporeal shock wave lithotripsy for solitary kidney or ureteral stones? J Urol. 2006;175:1370-3.
94. Kato Y, Yamaguchi S, Hori J, Okuyama M, Kakizaki H. Improvement of stone comminution by slow delivery rate of shock waves in extracorporeal lithotripsy. Int J Urol. 2006;13:1461-5.
95. Pishchalnikov YA, McAteer JA, Williams JC Jr, Pishchalnikova I, VonDerHaar RJ. Why stones break better at slow shock wave rate than at fast rate: in vitro study with a research electrohydraulic lithotripter. J Endourol. 2006;20:537-41.
96. Pishchalnikov YA, Sapozhnikov OA, Bailey MR, Pishchalnikova IV, Williams JC Jr, McAteer JA. Cavitation selectively reduces the negative-pressure phase of lithotripter shock waves. Acoust Res Let Online. 2005;6:280-6.
97. Pishchalnikov YA, Kaehr MM, McAteer JA. Influence of pulse repetition rate on cavitation at the surface of an object targeted by lithotripter shock waves. In: 2007 Proceedings of the ASME International Mechanical Engineering Congress and Exposition [DVD-ROM]. ASME International;2007:IMECE 2007-41387.
98. Eisenmenger W, Du XX, Tang C, Zhao S, Wang Y, Rong F, et al. The first clinical results of "wide focus and low pressure" ESWL. Ultrasound Med Biol. 2002; 28:769-74.