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

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Abstract

Shock wave lithotripsy (SWL) has proven to be a highly effective treatment for the removal of kidney stones. Shock waves (SW's) can be used to break most stone types, and because lithotripsy is the only non-invasive 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 effects¹. 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.

Keywords

lithotripsy; shock waves; urinary stones; kidney; injury; vascular trauma

The Advantages and Limitations of SWL

Shock wave lithotripsy employs high energy acoustic pulses (shock waves) generated outside the body to break stones within the kidney and ureter. As such SWL is the only non-invasive method available to remove stones. In the early years following its introduction SWL was considered an option for the treatment of virtually any stone type in any anatomical 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 is now 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)². Not all mineral types respond well to SW's. Some calcium oxalate monohydrate stones, brushite stones and a sub-type of cystine can be highly SW-resistant³. A noteworthy drawback of SWL is that in many cases stone fragments left behind can serve as foci for the development of new stones⁴. As such, stone free rates are lower and stone

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recurrence rates are higher for SWL than with invasive protocols such as ureteroscopy and percutaneous nephrostolithotomy that involve visual localization and extraction of stones 5. Still, because lithotripsy can be very effective, is non-invasive and is typically performed on an outpatient basis, SWL is used for the treatment of up to 70% of uncomplicated upper tract stone cases 6.

Lithotripters and Shock Waves

Lithotripters differ from one another in the method used to generate SW's (i.e. electromagnetic EML, electrohydraulic EHL spark gap, piezoelectric array), but they are largely the same in that they all produce a very similar acoustic pulse 7. Lithotripter SW's are characterized by a waveform having a leading positive pressure component of ~20–110 MPa followed by a negative pressure phase of ~–5–10 MPa (1 megapascal is ~10 atm pressure). The positive phase of the pulse is short lived (~1 μ s) 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 below). Most lithotripters have focal widths of ~6–10 mm, but some are quite narrow (\leq 4 mm) while 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 SW's 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 due to repetitive stress 8, 9. Shock waves create microcracks that progressively lengthen and expand until failure occurs. A variety of mechanisms have been proposed to explain how SW's break stones, but in simple terms this amounts to two main events, cavitation and direct stress 7. 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 SW's 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 10. 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 11. Thus, cavitation is critical to stone comminution, but also plays a major role in causing tissue damage (see below).

The large order fragmentation of stones is due to 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 12. 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 13. 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 14. 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. That is, since stone breakage is a progressive process it subjects the body to repetitive SW's (hundreds to thousands of SW's). It is also true that some of the same features of the lithotripter acoustic field that contribute to stone breakage are also 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^{15, 16}. 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, while suppression of the tensile phase of the SW, which is necessary to drive bubble growth, reduces tissue damage^{17–20}. 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^{19, 21}. 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 cavitation¹⁷. Whereas, 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 SW's to initiate cavitation in the kidney²². 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 acts as nuclei for bubble growth. However, what might serve as such a natural cavitation nucleus is unknown^{17, 23}.

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^{24, 25}. 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 damage²⁰. Thus, the cumulative shear model may be in good agreement with experimental results and may help explain why renal injury is reduced at slow SW-rate (see below)²⁶.

The Spectrum of Adverse Effects in SWL: Acute Renal and Extrarenal Damage Due to Shock Waves

Tissue damage in SWL most often involves trauma localized primarily to the region where the focal zone is targeted (i.e. the renal calyceal system), but can include injury to surrounding organs as well. 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 includes perforation of the colon, rupture of the hepatic artery, hepatic hematoma; pneumothorax, urinotorax, rupture of the spleen, acute necrotizing pancreatitis, dissecting abdominal wall abscess, rupture of the abdominal aorta, and iliac vein thrombosis, among others^{27–39}.

Virtually all patients who undergo SWL for renal stones exhibit hematuria after receiving about 200 SW's². 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 was also thought that hematuria was a consequence of irritation of the urothelium as stone fragments were broken by the SW's. However, animal studies soon showed that this was not the case. Detailed morphological studies in a variety of animals have shown that SW's rupture blood vessels and can damage surrounding renal tubules^{2, 15, 40, 41}. 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^{16, 42}. 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 sacrificed four hours following 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 2000 SW's with the Dornier HM3 lithotripter operated at 24 kV and SW's delivered at 120 SW/min produces a parenchymal lesion measuring ~5–6% of functional renal volume⁴³.

Perhaps the first indication of the potential for lithotripsy injury in patients came in an early report introducing lithotripsy as an alternative to open surgery⁴⁴. In that study subcapsular hematomas were observed by ultrasonography, but the occurrence was low—less than 1% of patients. Soon, a paper by Kaude et al reported a much higher hematoma rate (29%) in patients assessed by MRI⁴⁵. The Kaude report focused attention on the possibility that SW's could cause potentially significant injury. Numerous studies have since reported moderate to severe hemorrhage as a consequence of lithotripsy^{2, 15}. Case studies describe a variety of severe complications from intraparenchymal, subcapsular or perirenal bleeding, including irreversible acute renal failure^{46–54}. 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 membrane disease, likely as a consequence of glomerular injury during SWL⁵⁵. Values for hematoma rates range from less than 1% to about 20%, and depend on the type of lithotripter used and the radiological method and timing of the assessment^{49, 56, 57}. Age is an apparent risk factor in hematoma formation, with incidence increasing about two-fold per decade⁵⁸. Although some hematomas can persist for many months to years, it has been reported that most resolve within weeks and without long-term adverse effect⁵⁹. 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 effect.

The Potential for Long-term Adverse Effects Due to SWL: Hypertension, Diabetes, CaP Stone Disease

There has yet to be a definitive study performed with experimental animals, to fully characterize the manifestations of chronic injury in SWL. It is, however, clear that SW's 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 formation⁶⁰. Perhaps the first evidence of lasting SW injury was a study in dogs that showed dose-dependent parenchymal fibrosis at one month following treatment⁴⁰. Dose dependent scar formation, was also shown in rabbits in which scar volume increased nearly ten-fold by doubling the dose of SW's from 1000 to 2000 pulses⁶¹. 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 2000 SW's can show complete atrophy of renal papillae when the focal zone of the lithotripter is targeted within a lower pole calyx ².

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 preexisting 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.

A number of clinical studies have suggested that new-onset hypertension is a potential long-term consequence of SWL ^{1, 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 ⁵². 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 one month post-SWL ⁶⁸.

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, to of idiopathic calcium oxalate (CaOx) stone disease ^{70, 71}. One piece of this story follows the observation that over the past three 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 recently observed that a correlation exists between percent 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 SW's, and is often considered a contraindication for SWL (Figure 1).

It is well documented that SWL for treatment of stones within the kidney can cause extra-renal soft tissue damage (see above) ^{15, 38, 39}. 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 is typically 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's. 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 -1-2 MPa, and such pressures can be measured many centimeters off the acoustic axis ⁷. 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 has suggested that patients who underwent SWL for the treatment of kidney stones in 1985 were at increased risk of developing diabetes mellitus compared to controls ¹. Occurrence of diabetes in these patients was related to the total number of SW's and the power level of the lithotripter. The authors 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, while 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. This report has stimulated considerable discussion within the urology community ^{75, 76}. Like the data suggesting that multiple lithotripsies may be linked to an exacerbation of stone disease (see above), these findings are new and have as yet to be independently validated. Still, like 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 SW's delivered, the power setting of the lithotripter and the rate of SW delivery ⁷⁷⁻⁸⁴. 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's/min and higher were tested and found to create significantly more damage than the conventional rate of 60-120 SW/min ^{81, 82}. Cavitation and the potential for cumulative shear will both be enhanced as the SW rate is increased, so both mechanisms may well be involved in injury at extremely fast SW rates ^{7, 23-25}. Current practice is to treat patients at 60-120 SW/min and the vast majority of the literature on SWL adverse effects is for treatment in this range. Recent studies now show that slowing the SW rate to ~30 SW/min has a dramatic protective effect, and slow rate may be an important strategy for the future (see below).

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 ⁸⁵. 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 SW's ⁸⁶. History of a bleeding disorder is, indeed, considered a contraindication for SWL, as is a current course of anticoagulants or even aspirin ^{2, 53}. Age has been shown to be a factor in the occurrence of hematomas and in the development of new-onset hypertension following SWL ^{58, 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 a option for the treatment of children, there is evidence of delayed kidney growth in pediatric patients

treated by SWL^{2, 87, 88}. 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 dramatically accentuated in a pig model of pyelonephritis⁸⁹.

The Typical Treatment Protocol and New Strategies that Reduce SWL Injury

How SW's 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. Whereas 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 SW's, 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 SW's 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. Since stones are highly variable in their fragility to SW's it is difficult to estimate dose based on stone burden alone³. Progress has been made in using laboratory CT to predict fragility, but this must be further refined before it is useful at the clinical level⁹⁰. Because of this, patients may often be treated with the maximum number of SW's allowable for the lithotripter at hand (~2500–4500 SW's).

SWL injury is also dependent on power level but here too there is room for excess⁷⁹. 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 has shown that delivering SW's with a step-wise increase in power setting acts to reduce lesion size⁴³ (Figure 2). Injury was significantly reduced when treatment was initiated at 12 kV (first 100 SW's) followed by the remainder of the dose (2400 SW) at 24 kV, compared to all SW's at the high setting. This was the first indication that SW's could be used as the foundation for a strategy to protect the kidney from damage during further treatment. Treatment with a priming dose of low energy SW's induces transient vasoconstriction in both the treated and the contralateral kidneys⁷⁷. How vasoconstriction may contribute to protection is unclear, but this finding is an indication that the kidney is very responsive to focal stress.

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 are typically treated at a rate of 120 SW/min. A number of clinical studies have reported however, that slowing the SW-rate to 60–90 SW/min actually improves success rate^{91–95}. The acoustic mechanism for this effect involves cavitation. When stones are treated at fast SW-rate the surrounding fluid is charged with an increased number of minute microbubbles that persist between SW's and serve to seed cavitation with the next pulse⁹⁶. Thus cavitation is enhanced at fast rate compared to slow rate. Cavitation bubble growth occurs at the expense of negative pressure from the tensile phase of the SW, such that at fast rate the tensile phase of the pulse is sufficiently depleted to alter bubble cluster activity involved in stone breakage^{97, 98}.

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 2000 SW's (24 kV) at either 120 or 30 SW/min then processed for morphometric quantitation of the parenchymal lesion. The result was surprising²⁶. As expected from experience with earlier studies, the animals treated at the faster rate showed a parenchymal lesion occupying ~5% FRV. The pigs treated at the slower rate, however, had a vastly reduced lesion (<0.1% FRV) limited to renal papillae in the region of the focal zone of the lithotripter (Figure 2). Thus, slowing the rate of SW administration

significantly reduced tissue injury. A similar finding has recently been observed in a study to assess the renal injury produced by a novel electromagnetic lithotripter (XX-ES) with a very broad focal zone (~18 mm) 84. In that study pigs were treated at the same settings (1500 SW, ~17 MPa at 9.3 kV, 27 SW/min) used to treat patients with the XX-ES, and compared to animals treated with the same number of SW's at comparable settings (~32 MPa at 18 kV, 30 SW/min) with the Dornier HM3 lithotripter 99. Both groups showed extremely low injury. The HM3 group showed a barely detectable lesion (<0.1% FRV) while in the XX-ES group the lesion was too slight to quantify. Both of these experiments show 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) are also protective.

Summary: Shock Wave Injury and the Prognosis for Lithotripsy

It is clear that lithotripter SW's have the potential to cause tissue damage and that acute injury can lead to chronic adverse effects. Still, lithotripsy is the only non-invasive means to remove stones and this makes it particularly valuable. Injury, like stone breakage, is progressive and it typically takes hundreds of SW's 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 SW's 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 development of diabetes mellitus. The data for hypertension are the most compelling, while the data for transformation of stone disease are new and not as 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 recently been developed 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 will also be reduced, perhaps eliminated entirely.

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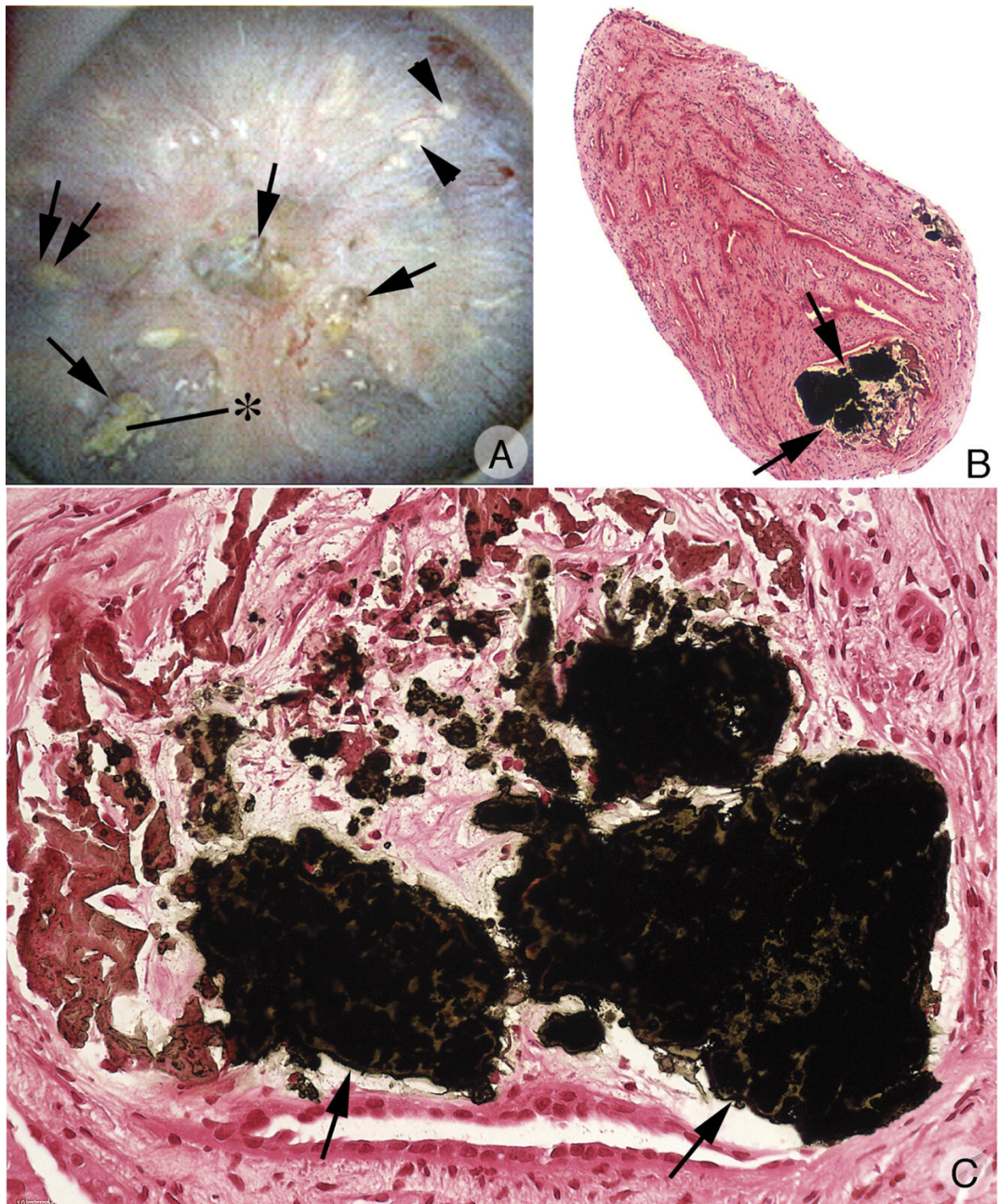


Figure 1.

Exacerbation of stone disease may be a consequence of SWL treatment. These images illustrate the morphological features of the renal papilla from a patient with brushite kidney stone disease. This patient received five SWL sessions prior to the onset of brushite stones. (A) Endoscopic view of a renal papilla showing three 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 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.

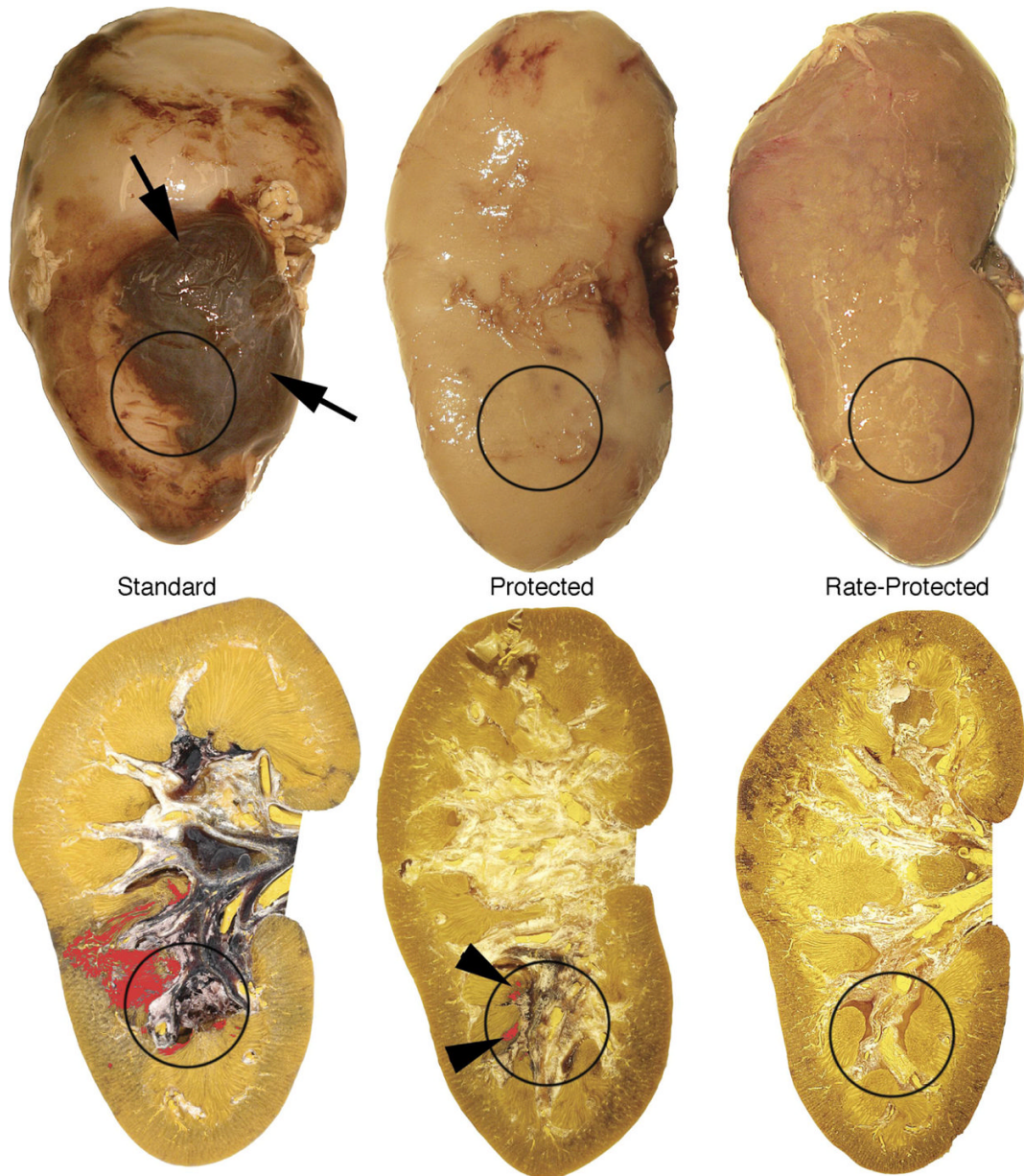


Figure 2. Demonstration that proper treatment strategies can protect against kidney injury in SWL. Top row shows exterior kidney surface, and bottom row shows macroscopic images of sections through three pig kidneys following different treatment protocols using the Dornier HM3 lithotripter (24 kV). Circles indicate 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 pig received 2000 SW's at 120 SW/min. Kidneys typically developed subcapsular hematomas (arrows). The hemorrhagic lesion in this kidney, determined from serial sections, measured ~5% FRV. (Middle) Protective effect of voltage ramping at standard rate. This pig received a priming dose of 500 SW's at low energy (12 kV) followed by 2000 SW's (24 kV) all at 120 SW/min. The lesion, limited to the tips of renal papillae (arrowhead), is dramatically reduced (~0.3% FRV) compared to the injury seen with the standard protocol. (Right) The protective

effect of slow SW-rate. This animal was treated with 2000 SW's delivered at 30 SW/min. No lesion is visible in this section. Injury at slow rate as determined from serial sections measured <0.1% FRV.

Table 1**Mechanisms of Shock Wave Action in SWL**

Stone Breakage

- Shear stress 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 SW's to initiate
 - Shear stress, enhanced at fast SW-rate, may break vessels leading to further cavitation
-

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

Table 3

Remarkable Renal Injury as a Consequence of SWL

- Intraparenchymal and subcapsular and 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

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, urinotorax
•	Perforation of bowel
•	Rupture of abdominal aorta, hepatic artery, iliac artery

Table 5

Treatment Strategies Shown to Reduce Renal Injury in Experimental Animals

<ul style="list-style-type: none">• Delivering fewer SW's• Reducing the power setting of the lithotripter• Pretreatment with SW's at low energy significantly reduces lesion size• Treatment at slow SW-rate (30 SW/min) virtually eliminates renal vascular injury
