WHITE PAPER

Current Perspective on Adverse Effects in Shock Wave Lithotripsy

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INTRODUCTION

In May 2006, a peer-reviewed paper published in *The Journal of Urology* reported the findings of a long-term follow-up study at the Mayo Clinic in which it was concluded that patients treated by shock wave lithotripsy (SWL) had an increased incidence of diabetes mellitus and were more likely to develop new-onset hypertension.[1] This report drew immediate attention in the popular press and sparked editorial comment in the urology literature.[2, 3] Although research dating back to the 1980s had established a link between SWL and hypertension in some patient groups, the Mayo Clinic report was the first to suggest diabetes mellitus as a potential long-term consequence of lithotripsy. At the present time, it is widely accepted among clinicians that SWL is a safe procedure, and that the complication rate and severity of adverse effects are minimal and tolerable considering the benefits of this entirely noninvasive therapy. However, it has long been recognized by researchers that shock waves (SWs) can cause injury to the kidney and that acute tissue damage due to SW treatment can be significant.[4-7] Now, with the possibility of chronic, life-altering adverse effects linked to lithotripsy, it is clear that the potential for long-term effects in SWL needs to be addressed.

As patient safety is a fundamental concern of the American Urological Association (AUA), a Task Force (Appendix 1) was established to provide expert opinion on the issue of adverse effects in SWL. The following report offers perspective on the current status of SWL with the goal of addressing three main questions 1) Is shock wave lithotripsy safe? , 2) Are the chronic adverse effects linked to SWL significant? , 3) Do the advantages of SWL outweigh the potential risks? This report focuses on clinical evidence. However, information from animal studies is reviewed to illustrate the tissue effects of shock wave energy.

CURRENT STATUS OF SHOCK WAVE LITHOTRIPSY

Shock wave lithotripsy was introduced as a clinical treatment for renal calculi by Chaussy and colleagues in Munich in 1980 utilizing a prototype device, the Dornier HM1 (for Human Machine).[8] The first widely distributed clinical lithotriptor, the Dornier HM3, was introduced to the United States in February 1984. This was followed by rapid acceptance of this noninvasive technology as a treatment alternative for renal and ureteral stones in the United States.

At the time of its introduction into clinical use, SWL was applied to a broad spectrum of upper urinary tract stone problems. With growing experience, urologists realized that there was a limit to the ability of the kidney and ureter to discharge stone fragments and, thus, the concept of stone burden (stone size and number) became important in selecting appropriate patients for lithotripsy. Currently, SWL is indicated for most uncomplicated upper urinary tract calculi; that is, an aggregate stone burden of <2 cm in kidneys with normal renal anatomy. Shock wave lithotripsy is also considered an appropriate alternative for the management of ureteral stones anywhere in the ureter with a few caveats (pregnancy, mid and lower ureteral stones in women of child bearing age).[9-11]

A number of factors can affect outcomes in SWL. For example, some mineral types (i.e., homogeneous cystine, brushite, some calcium oxalate monohydrate stones) are particularly resistant to fragmentation by SWs.[12] Renal anatomy can be problematic and in particular, stone location in the lower pole, the presence of renal anomalies (horseshoe kidney, calyceal diverticula, renal ectopy) and significant hydronephrosis all reduce SWL stone-free rates.[9] The effectiveness of lithotripsy is affected by body mass index, and studies indicate reduced outcomes when skin-to-stone distance is greater than about 10 cm.[14] In addition, outcomes for a given lithotriptor may be affected by factors such as the experience of the operator and the treatment protocol, but there is also evidence to suggest that some lithotriptors are less effective than others.[13, 15-19]

In summary, the advantages of SWL include its noninvasive nature, the fact that it is technically easy to treat most upper urinary tract calculi and that, at least acutely, it is a well tolerated, low morbidity treatment for the vast majority of patients. On the other hand the disadvantages of SWL are that retreatments may be necessary, and there appears to be a volume of fragments (when stone burden exceeds ~2 cm) that becomes problematic for the ureter to discharge.

LITHOTRIPSY ADVERSE EFFECTS

SHOCK WAVE LITHOTRIPSY TRAUMA TO THE KIDNEY: ACUTE EFFECTS AND MECHANISMS OF SHOCK WAVE INJURY

Animal studies have clearly established that SWs cause damage to the kidney vasculature.[4-6, 20] Morphological analysis of pig kidneys treated with a clinical dose of SWs has shown that veins are particularly susceptible to injury and that vascular damage occurs to a broad range of vessels, from vasa recta and cortical capillaries to intralobular and arcuate arteries and veins.[4, 6, 21, 22] Most animal research in SWL injury has been conducted using the Dornier HM3 electrohydraulic lithotriptor, but all lithotriptors studied have produced vascular damage.[23]

Shock wave lithotripsy can cause parenchymal bleeding and mild to severe subcapsular hematomas. Radiologic detection of hematomas in patients after SWL was perhaps the first indication of the adverse effects of SWs.[24] Although some hematomas persist, it is reported that most resolve without lasting adverse effect.[25] Large hematomas, while uncommon, are a potentially significant clinical event that may lead to blood transfusion and acute renal failure, fortunately rare events.[26-31] Hematoma rates may depend in part on the type of lithotriptor as values of less than 1% and up to 13% have been reported for different machines.[6, 32, 33] Understandably, detection of hematomas is higher when computed tomography or magnetic resonance imaging is used.[34, 35] Clearly, not all patients are equally at risk of developing hematomas. Increasing age has been identified as a risk factor for hematoma development. Excluding individuals with clotting abnormalities, it has been reported that the incidence of hematomas increases about two-fold per decade.[36]

Most of what is known about shock wave injury to the kidney comes from work with experimental animals where invasive methods can be used to assess for damage at the tissue level. The standard for assessment of SWL trauma to the kidney is quantification of hemorrhage in the parenchyma. Such bleeding within tissue cannot be observed by routine x-ray or CT and is not linked to the occurrence of hematomas. Thus, the absence of a hematoma by x-ray or CT does not rule out the occurrence of potentially significant trauma to the SWL-treated kidney.

Tissue damage in SWL is dose-dependent. Studies in experimental animals have demonstrated that lesion size (i.e., the volume of hemorrhagic tissue) increases with the SW number and with the power setting of the lithotriptor.[37-39]

The precise physical mechanisms responsible for tissue damage in SWL have yet to be determined. A variety of studies suggest that cavitation (bubble formation and collapse) is involved, but other mechanisms may be at play as well.[23, 40, 41] Evidence that cavitation is involved includes the observation of increased hemorrhage when micro-bubbles or gas-laden micro-beads are injected into the circulation during SWL.[42, 43] It has also been shown that strategies to suppress cavitation, such as using

tandem delayed SWs or a phase-reversed waveform to interrupt bubble growth, significantly reduce tissue damage.[44, 45] It is important to note that cavitation does not occur readily in circulating blood, and it can take hundreds of SWs to generate bubble activity within tissue in the living kidney.[43, 46] This suggests that cavitation may be highly dependent on the micro-environment of the vasculature. It is hypothesized that cavitation within blood vessels is dependent on the presence of minute particles that act as nuclei for cavitation bubble formation. It has yet to be determined what constitutes a natural cavitation nucleus in the circulation, but the fact that cavitation does not initiate readily suggests that the blood vascular system is relatively free of such particles.[43] Shock wave induced shear has the potential to damage tissue, and such a mechanism may contribute to injury, particularly at fast SW rates. In vitro experiments have shown that when isolated cells are held under static pressure greater than the threshold for cavitation, SWs cause more cell lysis than in untreated controls.[47] This suggests that cell injury occurs in the absence of cavitation. In an in vivo study, pigs were treated with SWs from a lithotriptor (Dornier HM3) fitted with a reflector insert that suppressed cavitation without significantly reducing SW amplitude. This dramatically reduced vascular injury compared to animals treated with the standard reflector, but these animals still showed a modest degree of bleeding involving vessels of the renal papillae.[45] A subsequent numerical modeling study suggests that stress can accumulate within kidney tissue if the SW rate is faster than the displacement relaxation time of the tissue.[48, 49] The model predicts that the magnitude of shear deformation of the renal parenchyma varies for different regions of the kidney, and the portion of the renal medulla (inner medulla) closest to the tip of the papilla, the area of the kidney that is most susceptible to SW injury, will undergo the greatest strain. This lends support to the idea that vessel rupture could be induced by shear and that subsequent bleeding could create an environment for cavitation, in turn creating further SW damage.

In summary, lithotriptor SWs can cause acute tissue injury, primarily damage to blood vessels. This hemorrhagic injury is dose-dependent and can be severe. Hematomas can occur as a consequence of SWL but do not serve as a reliable marker of SW injury. Cavitation is a likely mechanism for SW injury, but shear may be involved as well.

CHRONIC INJURY: THE POTENTIAL FOR LONG-TERM ADVERSE EFFECTS IN SWL

A critical issue, central to the theme of this report, is the question of whether SWL injury can lead to long-term adverse effects. The limited research that has been conducted in this area indicates that long-term effects do, indeed, occur as a result of SWL. Renal scar formation may develop after

SWL. This was demonstrated in patients using Single Photon Emission Computed Tomography (SPECT) to measure exclusion of Technicium-99 label from areas of poor vascular perfusion. [50] Patients scanned before and 30 days following SWL showed a loss of marker uptake, and scars that developed measured larger (mean 19x15 mm) than the focal zone of the lithotriptor that was used.

Studies with experimental animals also show that acute SW damage leads to scarring. Chronic damage of this sort was first reported in a laboratory study in which dogs treated with SWL showed fibrosis after one month, and the severity of scarring was dependent on the dose of SWs.[20] A study in rabbits, likewise, showed a dose-dependent increase in scar formation one month after treatment and a significant increase (nearly 10-fold higher) in scar volume with treatment at 2,000 SWs compared to 1,000 SWs. [51] The inner medulla of the kidney may be particularly susceptible to SW damage, and a study in juvenile pigs has shown that treatment with 2,000 SWs can lead to complete atrophy of the renal papilla at three months post-SWL.[9]

Although these manifestations of chronic injury have been identified, it seems likely that the full spectrum of long-term injury—the form and severity of chronic adverse effects—has yet to be determined. It is intuitive that chronic effects derive from acute tissue damage, but very little is known about the progression of tissue changes that link the two. There is also limited information about treatment dose and the development of chronic effects and whether specific risk factors exist that predispose an individual to long-term effects.

New-onset hypertension is a potential consequence of SWL, and evidence suggests that blood pressure changes following lithotripsy may be dose dependent.[6, 23] This topic has stimulated considerable debate, as not all findings agree, but the implications posed by reports showing a link between SWL and hypertension are cause for concern.[1, 52-59] A credible prospective study by Janetschek et al. showed an increase in intrarenal resistive index in patients 60 years of age and older.[52] This finding implies that SW treatment for stone disease can have serious, long-lasting effects, and that age could be a risk factor.[55] One can only speculate about what cellular level mechanisms might be at play; however, the observation that SWL can stimulate mesangial cell proliferation in pigs up to one month after treatment suggests a potential causative factor.[60]

A POTENTIAL LINK HAS BEEN IDENTIFIED BETWEEN SWL AND THE DEVELOPMENT OF DIABETES MELLITUS

The Mayo Clinic retrospective case-control study by Krambeck et al. evaluated the long-term effects of SWL on 630 patients with renal and proximal ureteral stones treated with SWL using the HM3 lithotriptor in 1985.[1] A survey was sent to those patients still living in 2004 (489 patients). Patients

were asked to report on new conditions that developed since their original SWL. Survey response rate was 58.9% (n=288). Responders were matched 1:1 with regards to age, gender, and year of presentation to a group of urolithiasis patients treated conservatively (i.e., no surgical intervention) who were continuing active follow-up.

The study found an increased risk of developing hypertension at long-term follow-up after SWL compared to the control group (Odds Ratio [OR] 1.47, 95% Confidence Interval [CI] 1.03 to 2.1, p=0.034). The development of hypertension was also associated with bilateral SWL treatments (p=0.033). An additional and potentially concerning finding was that patients treated with SWL were more likely to develop diabetes mellitus compared to controls at long-term follow-up (OR 3.23, 95% CI 1.73 to 6.02, p<0.001). This risk persisted in multivariate analysis controlling for presence of obesity in 2004 (OR 3.28, 95% CI 1.49 to 7.24, p=0.003) and change in body mass index over 19 years (OR 3.75, 95% CI 1.56 to 9.02, p=0.003). The development of diabetes mellitus in the SWL group was also associated with the number of shocks administered (p=0.005) and the total intensity of the treatment (p=0.007). A follow-up article from the same group noted stone recurrence in 154 (53.5%) of the 288 SWL patients treated in 1985 at 19 years follow-up.[61] Pre-existing diabetes mellitus was not associated with recurrent stone events (p=1.000); however, recurrent stone events were associated with the development of diabetes mellitus (p=0.020).

The authors noted limitations to the study and did not make causal claims; however, they offered possible explanation for their findings. Reference is made to prior reports of acute symptomatic pancreatitis after SWL, providing evidence that the pancreas can be affected by SWs.[62] In addition, there is reference to a study demonstrating elevated serum amylase, lipase and urinary amylase up to one week after SWL of proximal ureteral and renal stones, while these enzymes were not increased when lower ureteral stones were treated.[63]

The Mayo Clinic report stimulated commentary that has urged caution in interpreting the results, citing several methodologic biases in the study design.[2, 3] First, the control patients in the study represent a different patient population. Average stone size of the control group was 0.45 cm (0.1 to 2.0) compared to 1.08 (0.2 to 3.0) in the SWL group; thus, the control group is considered to have less severe stone disease than the SWL group. Differences in stone size were not controlled for in multivariate analysis. Second, family history, a known risk factor for the development of diabetes mellitus, was not reported for either cohort. Also, outcome data for patients treated with SWL were obtained through self-report while data for controls were collected through chart review, which has the potential to introduce collection bias. Although there was a good response rate to the questionnaire, it is possible that patients who experienced adverse events may have been more likely to respond than those who had not. In addition, it has been demonstrated that stone formers are already at increased risk of

developing diabetes mellitus and hypertension.[64, 65] Finally, the data from this manuscript reflects early SWL experience using a first-generation lithotriptor with a relatively wide focal zone and modest pressure amplitudes. It is uncertain as to whether these findings can be generalized to current practice using lithotriptors that have narrower focal zones. Without prospective randomized trials, studies on SWL are limited to retrospective reviews. However, when forced to work within the confines of a retrospective review, matched case-control comparisons can provide statistically sound data. In the Mayo Clinic study, the control group, although comprised of stone formers, had a different severity of disease compared to the SWL group. However, due to the accessibility and liberal use of SWL, it would be a difficult task to identify patients with symptomatic stones that have not undergone surgical interventions such as percutaneous nephrolithotomy or SWL. Ureterorenoscopy for symptomatic renal calculi may be used as a control group in the future, but not until ureterorenoscopy for renal calculi is widely available and used for 20 years can the same matched comparison be accomplished.

Two recent retrospective studies conducted after publication of the Mayo Clinic report have found no association between SWL and the development of diabetes mellitus. [66, 67] However, limitations in the experimental design of these studies leaves the question of potential for development of diabetes mellitus following SWL unanswered. [68] That is, in the study by Makhlouf and colleagues the duration of the follow-up period was only 6 years—likely too short a period to be relevant to the development of chronic disease. In the report by Sato and co-authors, follow-up was long-term (10-22 years, average 17 years) but the treatment dose was much lower (~900 SW) than is typically utilized around the world. As it is well established that tissue injury in SWL is dose-dependent the report of Sato and colleagues is unfortunately not particularly reassuring.

Until further studies of comparable design become available, the Mayo Clinic paper should be viewed as a warning of possible long-term adverse consequences of SWL, prompting further clinical and basic science translational research.

In summary, there is some evidence to suggest that long-term adverse effects of several types can develop as a consequence of SWL. Animal studies in particular suggest that the acute hemorrhagic lesion progresses to scar formation, resulting in loss of functional renal volume. Renal subcapsular hematomas can be long lasting but the medical consequences of this are unknown. A prospective study indicates that elderly patients are at increased risk of developing new-onset hypertension following SWL. In addition, a 19-year follow-up study has found an association between SWL and the onset of diabetes mellitus and hypertension.

TREATMENT STRATEGIES WITH THE POTENTIAL TO IMPROVE SWL

Recent studies show that changes in procedure and technique can improve SWL outcomes. Such advances include reduced tissue injury when the protocol includes a brief pause following the initiation of treatment, and both improved stone breakage and a reduction in injury when SWL is carried out at slow SW-rate.

PRETREATMENT PROTOCOLS HAVE THE POTENTIAL TO PROTECT AGAINST SWL INJURY

Studies in the pig model have demonstrated that treatment with a priming dose of low amplitude SWs reduces renal injury in SWL.69 Delivery of a dose of 2000 SWs with the Dornier HM3 lithotriptor using settings typical of clinical treatment (24 kV, 120 SW per minute) created a lesion measuring approximately 6% of functional renal volume (FRV). However, initiating treatment with as few as 100 low power SWs (12 kV) before completion of the dose with the higher amplitude pulses resulted in a significant reduction in the size of the lesion to 0.3% FRV. Recent research suggests that the power level of the priming dose is not the factor responsible for this protective effect, as the lesion volume was similar when the priming dose was delivered at 12, 18 or 24 kV.70 Instead, it was observed that inclusion of a three to four minute pause following the priming dose was protective, while increasing the power setting without this delay did not result in reduced injury. That is, injury was reduced only when the priming dose was followed by a brief delay. These findings are potentially important as they suggest a simple treatment strategy to reduce adverse effects in SWL.71 Such treatment protocols need to be confirmed in a clinical setting.

SLOWING THE SW FIRING RATE REDUCES RENAL INJURY AND IMPROVES STONE BREAKAGE OUTCOMES

Recent studies in pigs shows that slowing the firing rate of the lithotriptor to 60 SW per minute or slower reduces lesion size in the kidney to less that 0.1% FRV compared to ~6% FRV at 120 SW per minute.[72, 73] That is, slowing the SW rate results in protection against renal trauma similar to that observed using the low SW power pretreatment or pause-protection protocols.[69, 70] Such results from animal studies are encouraging, but similar studies have yet to be conducted with patients.

Stone breakage is affected by SW rate, and a number of clinical studies report that slowing the firing rate of the lithotriptor to 60 SW per minute gives better outcomes than treatment at the typical rate of 120 SW per minute.[74-79] This effect is seen with both electrohydraulic and electromagnetic lithotriptors. The advantage of slowing the SW rate is that fewer SWs are needed for treatment, but a potential disadvantage is a modest increase in overall treatment time.

CONCLUSIONS

We return to the main questions posed at the outset of this report.

IS SWL SAFE?

Since its introduction into the US in 1984, SWL has been performed with great success on millions of patients, but not unlike a surgical procedure, SWL carries the risk of unintended consequences. Shock waves have the potential to cause tissue damage and acute injury may lead to long-term adverse effects. There is likely a treatment threshold for initiation of SWL injury, but the upper limit for SW dose that can be delivered without causing vascular trauma is not known. It is highly likely that the vast majority of patients who are treated with a typical dose of SWs using currently accepted treatment settings experience some degree of acute renal trauma. It is not known if such injury sustained from a single treatment session alone leads to lasting damage. Animal experimentation demonstrates the severity of acute SWL injury. Whether or not acute SW damage progresses to long-term effects likely depends on SW dose (i.e., not only SW number but power, SW rate, and treatment sequence), as well as pathophysiologic risk factors that predispose the patient and/or kidney to a heightened response or particular pattern of response. The risk factors for acute SWL injury may not be the same as those for chronic effects. Thus, the safety of SWL depends on multiple factors that include the dose, treatment settings and acoustic characteristics of the lithotriptor used, frequency of retreatment, and a background of physiologic factors that may predispose the patient to increased risk of acute injury or progression to long-term damage. Recent studies with experimental animals demonstrating that renal injury is significantly reduced at slow SW rate or when a protective "pretreatment" protocol is used are very encouraging, and suggest that under proper conditions lithotripsy can be both safe and effective.

ARE THE CHRONIC ADVERSE EFFECTS LINKED TO SWL SIGNIFICANT?

Research to date suggests that SWL may lead to potentially significant chronic adverse effects including new-onset hypertension and diabetes mellitus. The long-term consequences of acute SW injury deserve further investigation.

DO THE ADVANTAGES OF SWL OUTWEIGH THE POTENTIAL RISKS?

Shock wave lithotripsy is often the best treatment option, in some settings may be the only treatment available and in most cases presents distinct advantages that outweigh the foreseeable risks. Like any of the stone technologies there are risks in using SWs, but it is also true that new treatment strategies are being developed that reduce adverse effects and improve stone breakage outcomes. Steps that

significantly reduce acute injury may have the potential to eliminate long-term adverse effects altogether. Still, limited understanding of the factors that lead to lasting injury after SWL calls for continued research on the mechanisms and consequences of SW injury.

CONFLICT OF INTEREST DISCLOSURES

All panel members completed Conflict of Interest disclosures. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

Consultant or Advisor: Dean G. Assimos, Altus (C); Robert I. Kahn, American Medical Systems (C); James E. Lingeman, Boston Scientific Corporation (C), Lumenis (U); **Board Member, Officer, Trustee**: Dean G. Assimos, Med Review in Urology, (C), Urology Times (C); Robert I. Kahn, California Urological Services (SF Lithotripsy, Ca. Prostate) (C); **Meeting Participant or Lecturer**: Robert I. Kahn, Astellas (C); James E. Lingeman, Boston Scientific (C), Lumenis (C); **Scientific Study or Trial**: James E. Lingeman, Boston Scientific (U), Olympus (U); Pei Zhong, Siemens Medical Solutions (C); **Investment Interest:** James E. Lingeman, Beck Analytical Laboratories (U), Midstate Mobile Lithotripsy, LP (U) **Other:** James E. Lingeman, Beck Analytical Laboratories (U), Midstate Mobile Lithotripsy, LP (U).

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