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SYMPOSIUM PAPER

A chronic outcome of shock wave lithotripsy is parenchymal fibrosis

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Abstract Shock wave lithotripsy (SWL) is widely viewed as an effective noninvasive method to break stones within the kidney and ureter. However, it is a technology that is not without trauma to the kidney—acute vascular, tubular and interstitial damage is often reported that if severe enough can lead to renal fibrosis (scarring) and permanent loss of functional parenchyma. These chronic changes can potentially lead to serious long-term adverse effects. The risk of developing chronic fibrotic lesions after lithotripsy is influenced by the number of shock waves (SWs) administered, SW power, rate of SW delivery and the number of SWL treatment sessions. The interplay between these risk factors is largely unknown, but progress has been made in identifying SWL protocols and pharmacologic therapies that can ameliorate the acute and chronic tissue damage that is an unintended consequence of SWL treatment.

Keywords Shock wave lithotripsy · Kidney · Fibrosis

Introduction

There are abundant reports in the literature that delivering shock waves (SWs) at clinical doses to break kidney stones will damage renal tissue, with one of the first signs of tissue trauma being hematuria [1]. Indeed, comprehensive morphological studies in a number of animal models have clearly shown that the primary acute lesion of shock wave lithotripsy (SWL) is vascular trauma leading to intraparenchymal hemorrhage, with initial breakage of small blood vessels largely within the medullary regions of the kidney that lie within the F2 focal zone of the lithotripter. As the applied SWs dose (number × power) is increased there is rupture of progressively larger blood vessels with the vascular lesion extending into the cortex towards the kidney surface producing focal sites of intraparenchymal hemorrhage [2]. Consequently, SWL can potentially result in perirenal and subcapsular hematomas, which in rare cases may be clinically significant and require surgical intervention [1]. Subsequent to blood vessel rupture and the pooling of blood, there is damage to tubules of the parenchyma including disruption of glomeruli, fracture of the basement membrane of cortical tubules, loops of Henle, and collecting ducts [2]. Increased excretion of renal tubular enzymes provides further evidence of tubular damage [3]. Numerous inflammatory cells migrate to sites of injury immediately after SWL—including platelets and leukocytes that line injured blood vessel walls and infiltrate surrounding damaged tubules and interstitial cells [2]. This SWL-induced acute inflammatory response has a rapid onset (within 30 min) and has been referred to as "lithotripsy nephritis". There is production and release of proinflammatory cytokines and injurious molecules (e.g. iron/reactive oxygen metabolites; vasoconstrictor peptides/ischemia; metabolic toxins) that are largely localized in the SW-exposed tissue [4–7].

At the same time that these injurious agents create havoc within the cell, they also set in motion a series of complex cellular and molecular events that serves to contain the damage. In most instances, tissue repair involves (1) regeneration of injured cells by cells of the same type and (2) replacement by connective tissue, called fibrosis, which leaves a permanent scar and permits the residual

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parenchyma to continue functioning. Renal fibrosis represents a failed wound-healing process that leads to excessive accumulation and deposition of extracellular matrix components, usually collagen, in response to chronic, sustained inflammation [8, 9]. An aggressive fibrogenic response is itself deleterious and may further injure the kidney it is attempting to protect by engulfing and destroying more glomeruli, tubules, and microvessels—thereby promoting the release of more cytokines that stimulate more scar formation and an additional loss of functional tissue [9].

A variety of chronic changes occur in the kidney after SWL, some of which can be classified as (1) reversible injury that resolves within days to several weeks after SWL (e.g. mild tubular necrosis, vacuolar changes of the tubular epithelium, mild interstitial edema or hemorrhage), or (2) irreversible injury which involves tissue damage detectable beyond several weeks post-SWL (e.g. perivascular/interstitial fibrosis and permanent loss of functional parenchyma) [2]. Although little is known of the progression from SWL-induced acute injury to permanent damage, there is evidence that many of the same SW delivery factors that affect acute renal injury can also influence the severity of long-term renal damage.

Effect of SW number on renal parenchymal fibrosis

Kidney biopsies taken from SWL-treated patients have shown that SW therapy can result in fibrotic lesions within the cortex and medulla [10]. Lechevallier et al. used ^{99}Tc-DMSA and single photon emission computed tomography to quantify the SWL-induced fibrotic lesion in patients treated with 2,100–6,000 SWs from the EDAP LT-01 lithotripter. They found at 30 days post-lithotripsy that renal scarring was evident in 6 of 12 patients, but that the incidence and size of renal scarring was not correlated with SW number [11]. However, animal studies in which the SWL-treated kidney can be harvested and processed for parenchymal injury have clearly shown that increasing the number of delivered SWs results in an increased amount of renal fibrotic tissue. Morris et al. [12] treated uni-nephrectomized anesthetized rabbits with 1,000 SWs or 2,000 SWs using the Wolf Piezolith 2300 lithotripter, and demonstrated 30 days later that doubling the number of SWs delivered to the kidney resulted in a ninefold increase in the fibrotic lesion (1.37 vs. 12.76% of renal volume damaged). The authors are to be commended for their careful attempt to quantify the fibrotic lesion, but the amount of renal parenchyma lost to fibrosis might be underestimated due to sites of scarring undergoing contraction/shrinkage in size over time. Indeed, the majority of SWL studies that report renal fibrosis have been qualitative in nature. One month after treating anesthetized dogs with 1,600 SWs using the Dornier HM3 lithotripter, kidneys had small patches of fibrosis present at the corticomedullary junction, whereas more extensive interstitial fibrosis with dense hyalinized acellular scars spanning the cortex and medulla were present in kidneys treated with 8,000 SWs [13]. Similarly, rabbit kidneys treated with 1,000–3,000 SWs from the MPL 9000 lithotripter demonstrated a higher incidence of capsular and interstitial fibrosis at the higher SW exposure at 2 months post-SWL [14]. MRI and/or histological evaluation of rat kidneys after treatment with 500–5,000 SWs using the HM3 lithotripter showed evidence of fibrotic shrinkage of the renal parenchyma at 2–5 weeks post-lithotripsy—the severity being correlated dose dependently with the number of SWs delivered [15, 16]. Therefore, animal studies would suggest that it is best to avoid administering large doses of SWs so as to minimize potential long-term damage to the parenchyma.

Effect of SW voltage on renal parenchymal fibrosis

Rassweiler et al. used anesthetized dogs to evaluate the acute and chronic renal trauma effects of SWL using the Modulith SL 20 at differing generator voltages. They found that delivery of 2,500 SWs at 13 kV to the kidney produced an acute Grade 1 lesion (petechial medullary hemorrhage and minor tubular cell necrosis) with no discernable long-term sequelae at 10 weeks post-lithotripsy. However, delivery of the same number of SWs at 17–20 kV produced a more severe acute Grade 3 lesion (perirenal and cortical hematoma, major tubular cell necrosis) that progressed to segmental fibrosis and focal thickening/fibrosis of the renal capsule at 10 weeks [17]. These findings highlight the fact that long-term parenchymal damage appears related in some fashion to the degree of acute trauma—although, little is known about the threshold of acute damage that leads to a permanent change.

Effect of SW rate on renal parenchymal fibrosis

Acute parenchymal damage and hemorrhagic lesions are more severe at higher rates of SW delivery [18, 19]. Therefore, it is not unexpected that SW delivery rate has also been implicated as a factor influencing the severity of the chronic lesion, with higher SW rates associated with a greater amount of renal parenchymal fibrosis [20].

Effect of multiple SWL sessions on renal parenchymal fibrosis

Although there is abundant evidence that a single session of SWL can result in renal scarring—particularly in animal

models, it is less clear whether the fibrotic lesion is influenced by multiple SWL sessions. This is an important issue because more than one SWL session is sometimes needed to adequately fragment a renal stone(s), and patients with recurrent episodes of kidney stones may receive multiple SWL treatments. Treating five uni-nephrectomized rabbits with two sessions of SWL of only 1,000 SWs (1,000 bar at 90 SWs/min delivered from the Wolf Piezolith 2300) each, to the same renal pole and separated by 1 week, resulted in a renal fibrotic lesion that was statistically similar in size to the lesion in five rabbits treated with 1,000 SWs in a single SWL session (2.80 ± 1.2 vs. 1.37 ± 1.0% of renal volume damaged, respectively) [12]. Others have reported that the amount of renal parenchyma that is fibrotic increases after multiple SWL sessions using either a morphological grading system of cell damage or were purely descriptive [20, 21], and that the accumulation of chronic damage was more extensive if higher SW frequencies were used [20]. Overall, the experimental evidence supporting the view that permanent tissue damage accumulates after multiple lithotripsy sessions is weak, and further investigation is needed.

Effect of lithotripter type on renal parenchymal fibrosis

A variety of lithotripter types have been shown to cause permanent morphological changes in kidneys treated with a clinical dose of SWs (see above). However, few studies have compared the chronic morphological changes generated by different types of lithotripter. One such study was by Morris and colleagues [22] who employed uni-nephrectomized anesthetized rabbits to compare the renal damage induced by three lithotripters with different modes of SW generation: electrohydraulic (Dornier HM3, 500 SWs at 21 kV), electromagnetic (Siemens Lithostar, 1,250 SWs at 19 kV), and piezoelectric (Wolf Piezolith 2300, 1,000 SWs at 1,000 bars). SW power settings were chosen to approximate that used clinically with SW number reduced by 75% to account for the significantly smaller size of the rabbit kidney compared with the human kidney. There was a transient increase in urinary excretion of renal injury markers (*N*-acetyl-D-glucosaminidase and γ-glutamyl transferease) after SWL over a 28-day period, and was similar for all lithotripters. However, distinct differences in the pattern of acute and chronic changes in renal morphology were noted between lithotripters. Acute histological evaluation of kidneys treated with SWs from electrohydraulic and electromagnetic lithotripters revealed extensive and large subcapsular hematomas with intratubular hemorrhage and punctate cortical and medullary necrosis that subsequently developed into chronic subcapsular fibrosis. This is in contrast to an acute central focal area of parenchymal hemorrhage and tubular destruction with relatively minimal subcapsular and intratubular hemorrhages noted in kidneys treated with the piezoelectric lithotripter. The small focal zone and high acoustic pressures generated by the piezoelectric machine were presumably responsible for this highly focal site of severe parenchymal damage, which evolved into a chronic necrotic core with a surrounding densely fibrotic reaction and extended into the adjacent renal parenchyma. Although the amount of renal parenchymal fibrosis was similar in all three lithotripters, the fibrotic lesion that resulted from piezoelectric lithotripter treatment was clearly more localized and—although, not stated in the publication—may have resulted in greater medullary parenchyma fibrosis. The biological implication of this, if any, is unknown, but it is noteworthy that the medulla is important in the regulation of blood pressure, urinary concentration and dilution, and urinary acidification [23–25]—functions that can potentially be influenced by SWL treatment [26, 27].

The potential for long-term adverse effects caused by SWL

Although animal studies convincingly demonstrate that the kidney treated with SWs is susceptible to permanent parenchymal damage, the important issue is whether this is clinically relevant—a topic of continuing discussion and controversy. The permanent loss of parenchymal tissue will undoubtedly precipitate pathological consequences at some point when enough functional tissue has been lost. The potential for such long-term adverse effects of SWL have been discussed in recent reviews and will not be addressed here, but include an accelerated rise in systemic blood pressure, new-onset hypertension, a decrease in renal function, an increase in the rate of stone recurrence and brushite stone disease, and the development of diabetes [1, 28].

Protective strategies

Acute injury appears to be a prerequisite for chronic changes to the kidney. Therefore, if the acute renal injury that results from SWL can be prevented or reduced, then there is the expectation that any resulting long-term parenchymal lesion and associated adverse outcomes will also be reduced. One strategy to reduce the renal fibrotic lesion induced by SWL is to modify the manner that SWs are delivered, e.g., reducing the number of applied SWs, using SWs that are less powerful, slowing the SW delivery rate (see above). Treating the kidney with SWs and then a

brief pause prior to high-energy SWL treatment is also known to reduce acute injury [29, 30], and it remains to be determined whether delivery of SWs in this fashion will be associated with less fibrotic lesions. A great deal of attention has been focused on pharmacologic therapies to reduce the acute and chronic injurious complications of SWL. Calcium channel blockers, anti-inflammatory agents, and antioxidants have all been shown to reduce the injury that results from SWL [31–33]. Nearly all of this body of work has involved either measurement of renal injury markers and/or histologic scoring of renal damage, and shown that such drug treatments resulted in an improvement in cell integrity, a reduced inflammatory and oxidative stress response, and lower levels of tubular injury markers in the urine measured days or weeks after SWL. One of the few studies that estimated the amount of renal fibrosis after SWL reported that allopurinol (antioxidant) was particularly effective as a protective agent in SWL-treated rabbits [34]. Reduced urinary markers of tubular injury were observed in rats given the anti-inflammatory COX-2 inhibitor, celecoxib (10 mg/kg per day for 1 week), before SWL [35]. An advantage of giving a COX-2 inhibitor before and after SWL is not only the renal protective effect, but also reducing the SWL associated pain due to the drug's analgesic properties.

Li and colleagues performed a prospective randomized clinical trial to determine the effects of nifedipine (Ca channel antagonist) and allopurinol on 40 SWL-treated patients. To determine the level of SWL-induced renal injury, they measured several glomerular and tubular markers in the urine before, 1 and 3 days after SWL. Administrating the medications alone or in combination significantly reduced the levels of these markers compared with SWL alone, indicating that they had a protective effect. The authors suggested that each of these medications could have reduced tissue injury, in part, by blocking a pathway of oxidative stress [36]. In contrast, patients given an oral antioxidant formula (containing higher than the daily recommended dose of vitamins A, C, E, zinc and selenium) were reported to have reduced levels of renal injury markers in blood after SWL, but paradoxically not in urine [37, 38], and therefore it is unclear whether such an oral antioxidant regimen was effective in ameliorating SWL-induced renal injury. Others have reported that verapamil (Ca channel antagonist) and mannitol protect patients from SWL-induced renal injury as evidenced by reduced urinary renal injury markers [39, 40]. Therefore, the majority of both clinical and experimental evidence indicates that a number of drugs have the potential for ameliorating SWL-induced renal injury.

Other possible tissue-protective strategies include the development of instrumentation that will allow SWs to be delivered to the stone only when the stone is within the focal zone of the lithotripter, as well as monitoring the progress of stone fragmentation. Advancements on these and other technologic fronts [41] will likely help decrease the incidence of patients being over-treated with SWs—thereby, reducing the potential for both acute and chronic SWL-induced tissue injury.

Summary

SWs can damage renal tissue, and if the damage is severe enough will lead to tissue fibrosis and the permanent loss of parenchymal tissue. It is perhaps not surprising that many of the risk factors for SWL-induced acute tissue injury are similar to those for the progression of tissue injury to fibrosis. Research continues in improving the way that SWs are delivered to the kidney to efficiently fragment kidney stones whilst reducing potential side effects of tissue injury, as well as developing pharmacologic therapies to reduce SWL-induced tissue injury.

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