Assessment of Renal Injury With a Clinical Dual Head Lithotriptor Delivering 240 Shock Waves per Minute

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Abbreviations and Acronyms

EPAH = PAH renal extraction
ERPF = effective renal plasma flow
FRV = functional renal volume
GFR = glomerular filtration rate
MRI = magnetic resonance imaging
PAH = para-aminohippuric acid
SW = shock wave
SWL = shock wave lithotripsy

Submitted for publication February 25, 2008.
Supported by National Institutes of Health Grants DK43881 and DK067133.
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Purpose: Lithotriptors with 2 treatment heads deliver shock waves along separate paths. Firing 1 head and then the other in alternating mode has been suggested as a strategy to treat stones twice as rapidly as with conventional shock wave lithotripsy. Because the shock wave rate is known to have a role in shock wave lithotripsy induced injury, and given that treatment using 2 separate shock wave sources exposes more renal tissue to shock wave energy than treatment with a conventional lithotriptor, we assessed renal trauma in pigs following treatment at rapid rate (240 shock waves per minute and 120 shock waves per minute per head) using a Duet lithotriptor (Direx Medical Systems, Petach Tikva, Israel) fired in alternating mode.

Materials and Methods: Eight adult female pigs (Hardin Farms, Danville, Indiana) each were treated with sham shock wave lithotripsy or 2,400 shock waves delivered in alternating mode (1,200 shock waves per head, 120 shock waves per minute per head and 240 shock waves per minute overall at a power level of 10) to the lower renal pole. Renal functional parameters, including glomerular filtration rate and effective renal plasma flow, were determined before and 1 hour after shock wave lithotripsy. The kidneys were perfusion fixed in situ and the hemorrhagic lesion was quantified as a percent of functional renal volume.

Results: Shock wave treatment resulted in no significant change in renal function and the response was similar to the functional response seen in sham shock wave treated animals. In 6 pigs treated with alternating mode the renal lesion was small at a mean ± SEM of 0.22% ± 0.09% of functional renal volume.

Conclusions: Kidney tissue and function were minimally affected by a clinical dose of shock waves delivered in alternating mode (120 shock waves per minute per head and 240 shock waves per minute overall) with a Duet lithotriptor. These observations decrease concern that dual head lithotripsy at a rapid rate is inherently dangerous.

Key Words: kidney, lithotripsy, swine, instrumentation, high-energy shock waves

New concepts in lithotriptor design have emerged that include SW delivery from dual treatment heads.[1–5] The Duet lithotriptor has 2 independent spark plug generator/reflector systems at a 72-degree angle to each other, such that SWs from each treatment head converge at a common focal point. This machine is approved in the United States for patient treatment in synchronous/simultaneous (2 heads are fired simultaneously) or asynchronous/alternating (firing alternates between the 2 heads) modes

0022-5347/09/1812-0884/0
THE JOURNAL OF UROLOGY®

Vol. 181, 884-889, February 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2008.10.065

at up to 120 SWs per minute per head. A potential benefit of dual head firing in alternating mode is that the stone can be exposed to 240 SWs per minute and, thus, a given dose of SWs can be delivered in half the time.

Safety is an important issue in SWL. Numerous reports have described SW induced renal trauma in patients and there is growing awareness of a link between acute tissue damage and the potential for long-term adverse effects.[6–9] Studies in experimental animals have characterized acute SWL trauma as primarily a vascular lesion that can trigger an inflammatory response leading to parenchymal scarring and loss of functional renal mass.[10,11] The hemorrhagic lesion is focal in the sense that tissue damage is most pronounced in the region of the kidney targeted by the focal volume. That is, injury occurs along the acoustic axis, along the SW path through the kidney. In SWL with a conventional lithotriptor this can be seen to produce tissue damage extending from the renal papilla through the full thickness of the medulla and cortex.[10,11] In treatment using a dual head lithotriptor SWs follow 2 paths through the kidney, raising the possibility that a greater volume of kidney tissue may be subjected to injury.

The rate of SW administration has emerged as a potentially important factor in SWL injury. A rapid SW rate has been shown in experimental animals to enhance injury[12,13] and a recent study demonstrated that slowing the SW rate to 30 SWs per minute significantly decreases lesion volume compared to treatment at 120 SWs per minute.[14] With this in mind it seems important to assess the safety of SW exposure at the increased rate of 240 SWs per minute that occurs with dual head lithotripsy in alternating mode.

To our knowledge we report the first study of the renal bioeffects of a clinical dose of SWs delivered in asynchronous/alternating mode using a Duet lithotriptor in an established in vivo porcine model that is commonly used in SW research.[15,16]

METHODS AND MATERIALS

Adult female pigs weighing 45 kg were rendered unconscious with an intramuscular injection of ketamine (15 to 20 mg/kg) and xylazine (2 mg/kg) with anesthesia maintained with 1% to 3% isoflurane and 100% oxygen. The animals were prepared for renal function measurements as previously described, including catheter placement into the ear vein for the intravenous infusion of fluids, the infrarenal aorta for blood pressure and heart rate monitoring and arterial blood sampling, each renal vein for renal venous blood sampling and each ureter for urine collection.[16] Saline (150 mmol/l) was infused intravenously at 1% body weight per hour throughout the experiment to maintain adequate hydration and urine flow.

Duet Lithotriptor Experimental Protocol

The pig was placed supine on the adjustable lithotriptor treatment table. Baseline cardiovascular and renal function measurements, which were begun 30 minutes following the completion of all surgery and coupling with castor oil of the pig to the lithotriptor SW generator heads, consisted of 2, 25-minute clearances. The lithotriptor was targeted on the left kidney lower pole calix under fluoroscopic guidance with a small amount of contrast medium injected through the left ureteral catheter. Eight animals each underwent no SWs (group 1) or 2,400 SWs (group 2) at 1,200 SWs per head, 120 SWs per minute per head and 240 SWs per minute overall at a power level of 10. The latter is recommended for clinical treatment in alternating mode. Lithotripsy was temporarily halted every 500 SWs to confirm targeting. Three 25-minute clearances were then obtained after a 30-minute post-lithotripsy recovery period.

Renal Function Measurements

Inulin and PAH were intravenously administered as a bolus, followed by infusion at 70 ml per hour to achieve a steady state plasma concentration of 20 and 2 mg/dl, respectively. Plasma and urine samples were analyzed for inulin and PAH and their renal clearance was used as an estimate of GFR and ERPF, respectively. EPAH was calculated using the formula, $(PAH_{arterial} - PAH_{renal\ venous})/PAH_{arterial} \times 100$, providing an estimate of the efficiency of renal tubular organic anion transport.[16]

Morphological Analysis

The kidneys were perfusion fixed in situ at the end of the experiment and removed for histological and quantitative morphological analysis, as previously described.[17] Hemorrhagic regions in the parenchyma were identified and expressed as a percent of FRV using computer assisted segmentation of digital images from 120 μm serial sections of the entire kidney. The smallest lesion that can be accurately measured with this system is 0.1% FRV.

In Vitro Stone Breakage Studies

Experiments were done in a test tank fitted with 2 latex acoustic windows that were coupled to the treatment heads using castor oil.[18] The tank was filled with tap water, which was then degassed with a pinhole degasser to maintain gas content at about 2 mg/l (approximately 20% of saturation). The focal point of the lithotriptor was identified using the device alignment stylus and then marked by crossed lasers. All studies were performed with artificial Ultracal® 30 gypsum stones placed in a 2 mm mesh metal wire basket positioned at the focal point.[19] SWs were administered in alternating (asynchronous) mode at 120 SWs per minute per head and 240 SWs per minute at a power level of 10 in 26 stones and in simultaneous (synchronous) mode with dual SWs at 120 SWs per minute per head at a power level of 5 in 20 stones. Stone breakage was assessed by counting the number of SWs needed to remove all stone material from the basket. Different power settings were used in the 2 modes, including power level 10 for alternating mode and power level 5 for simultaneous mode, because these settings are recommended for clinical treatment.

Statistical Analysis

All values are presented as the mean ± SEM. Comparison of renal function in and across groups was done with 2-factor ANOVA with repeated measures. Stone breakage analysis was done using the unpaired Student t test. Differences between means were considered significant at the 5% level.

RESULTS

Cardiovascular Measurements

Blood pressure and renal responses to dual pulse SW application were similar to those observed in sham SW treated animals. A small time related 6 to 10 mm Hg decrease in mean arterial pressure was seen with no significant alteration in GFR, ERPF or EPAH (fig. 1). Likewise renal filtration and perfusion, and tubular PAH transport were unaltered in the contralateral untreated kidney in each group (data not shown).

Morphological Measurements

Visual examination of the kidney anterior and posterior surfaces revealed small focal sites of subcapsular bleeding in 5 of the 8 Duet treated kidneys. The 3 remaining SW treated kidneys were similar to sham SWL treated kidneys in that they showed no evidence of subcapsular hemorrhage.

Hemorrhagic lesion size was quantified in 6 SW treated kidneys. The degree of intraparenchymal hemorrhage induced by lithotripsy was 0.22% ± 0.09% FRV ($p = 0.0502$), that is no detectable lesion in 2 kidneys, a focal papillary lesion in 1 (less than 0.1%) and small discrete lesions in the papillae and cortex of 3 (0.37%, 0.40% and 0.46%, respectively). No tissue damage was observed in sham SWL treated pigs. Figure 2 shows 3 consecutive unstained 5 mm cross sections of an SWL treated kidney. Lesion sites appeared to correlate with the SW path from the upper and lower treatment heads when these cross sections were overlaid on the MRI image of a pig and the superimposed location of the dual treatment heads.

In Vitro Stone Breakage Studies

Stone breakage in alternating mode required 679 ± 24 SWs compared to 601 ± 35 SWs (approximately 300 dual SWs) delivered in simultaneous mode. Because the SW rate of 120 SWs per minute of the 2 treatment heads was the same in alternating and simultaneous modes, overall treatment time was 170 and 150 seconds, respectively. These results suggest a trend toward a slightly higher (approximately 13%) total SW number and treatment time for stone comminution in alternating vs simultaneous mode (each $p = 0.0666$).

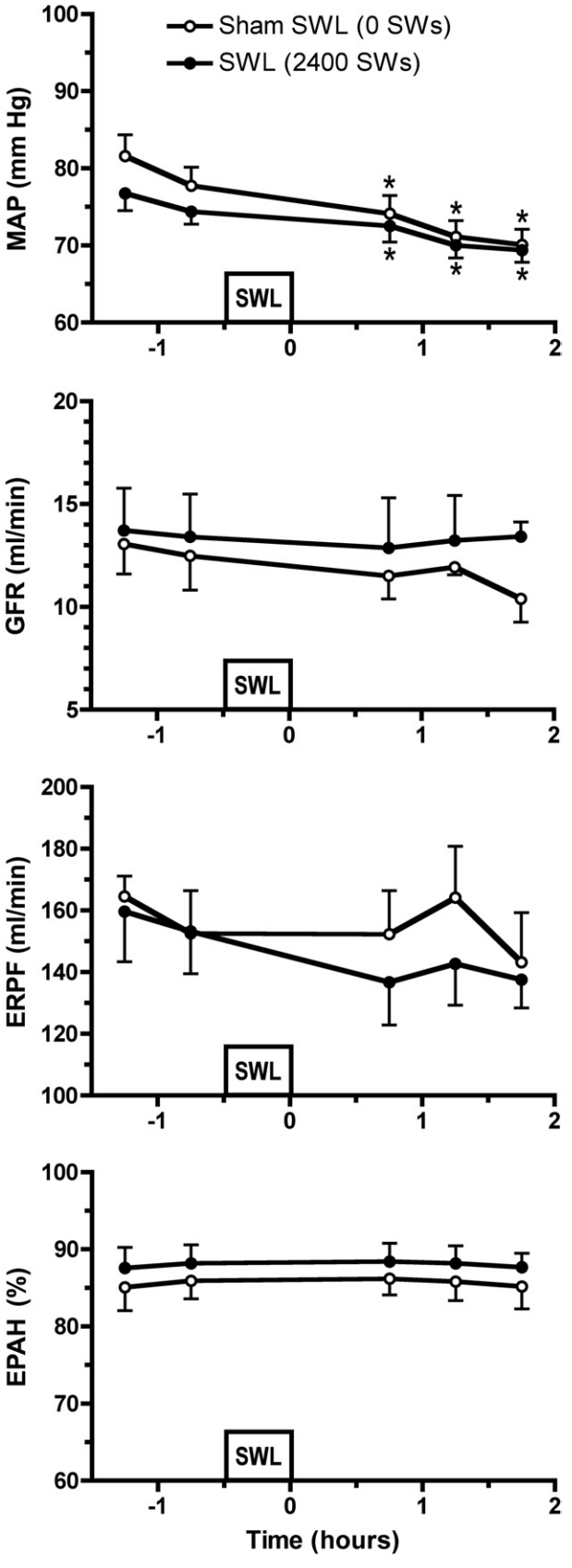

Figure 1. Blood pressure and renal responses in sham SWL and SWL treated kidneys. *MAP*, mean arterial pressure. Asterisk indicates $p < 0.05$ vs pretreatment values.

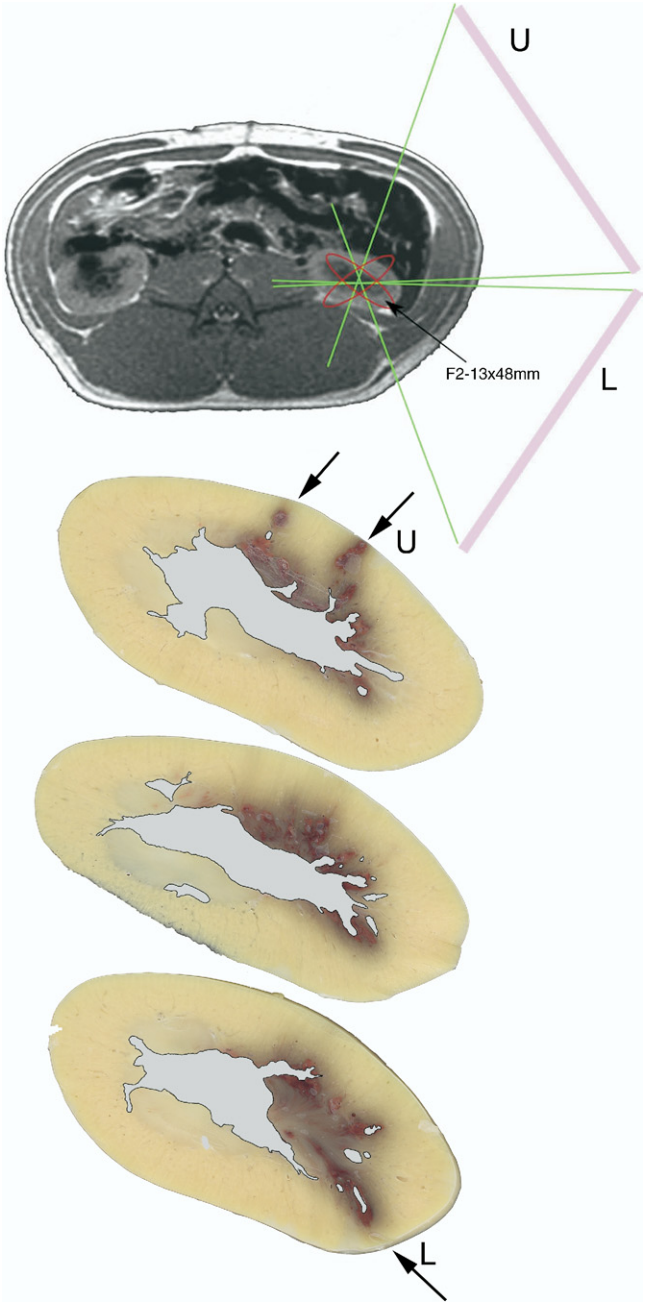

Figure 2. MRI of pig at level of both kidneys with superimposed location of upper (*U*) and lower (*L*) treatment heads, and 3 serial unstained 5 mm cross sections of Duet treated kidney. Focused SW was targeted onto left kidney lower pole calix. Reddish brown areas indicate lesion areas (arrows) in cross sections of SW treated kidney. Lesion sites appeared to correlate with SW path from upper and lower treatment heads when these cross sections were overlaid on MRI of pig with superimposed treatment head location. Gray areas indicate renal sinus region. Cross sections at ×2 magnification.

DISCUSSION

An important motivation for the current study was concern that delivering SWs to the kidney at the combined SW rate of 240 SWs per minute (120 SWs per minute per head) might enhance tissue damage. Results show otherwise. It has been noted in animal studies with single head lithotriptors that treatment at a slow SW rate of 30 SWs per minute produces little injury[14] and treatment at an extremely rapid rate of 900 SWs per minute or greater causes dramatically increased tissue damage.[12,13] The lesion produced by 2,400 SWs (1,200 SWs per head at a power level of 10) at 120 SWs per minute in alternating mode was quite low at 0.22% ± 0.09% FRV, which compares favorably with the 1.08% ± 0.38% FRV lesion produced by 2,400 SWs delivered with the Dornier® HM3 lithotriptor at 120 SWs per minute and 24 kV.[18]

The injury observed in this study using SWs fired in alternating mode was statistically similar, even if somewhat lower, than in a previous study in which SWs were delivered as simultaneous dual pulses (0.22% ± 0.09% vs 0.96% ± 0.39% FRV, $p = 0.1044$).[18] These results are difficult to compare directly since treatment conditions were different. Whereas in alternating mode the SWs fired from the 2 treatment heads arrive at the focal point independently, the SWs fired in simultaneous mode intersect at the target. These coincident SWs produce a focal zone in which acoustic pressures are doubled. In addition, in simultaneous mode the kidney location of the combined focal zones depends on the timing of the 2 SWs, such that this zone shifts in position throughout treatment.[18] Regardless of these differences it seems noteworthy that the injury observed in each mode was indeed quite slight. A potential explanation is related to the efficiency of acoustic coupling in dry head lithotriptors. In vitro studies have shown that air pockets at the coupling interface of a dry treatment head can dramatically decrease SW energy transmission.[20] Even under ideal conditions in vitro it is difficult to attain coupling that is free of defects and having 2 treatment heads could only compound the difficulty with achieving good coupling. However, to our knowledge there is currently no means to determine the quality of coupling with any dry head device and, thus, there was no way to assess coupling in this study of the Duet lithotriptor. The coupling protocol used in these experiments in pigs followed the accepted clinical protocol for this device. Thus, in regard to coupling the results may well be consistent with what occurs during patient treatment.

A potentially important aspect of these studies of renal injury in pigs using the Duet and HM3 lithotriptors involves the sequence that was followed for SW delivery. In particular it should be noted that treatment was not continuous and periodic pauses were built into the treatment protocol to assess alignment and targeting. Recently we observed that a brief pause in treatment can have a protective

effect, acting to decrease the severity of renal injury.[21,22] For example, when pigs were treated with a priming dose of 100 SWs at 24 kV with the HM3, followed by a 3-minute break before the main dose of 2,000 SWs was delivered, injury was significantly decreased compared to treatment with the main SW dose alone (0.51% ± 0.14% vs 3.93% ± 1.29% FRV, $p = 0.0135$).[22] In regard to the current and previous studies of the Duet lithotriptor as well as background data cited on the HM3 device it is important to recognize that the renal injury values pertain only to the specific treatment protocols that were followed. Because pauses in SW treatment could potentially evoke a protective response, one might predict a higher level of injury with the Duet and HM3 devices if treatment were continuous. Thus, it seems prudent to use a brief 3 to 4-minute pause in SW delivery as part of the treatment protocol regardless of the type of lithotriptor used.

A potential advantage of dual pulse lithotripsy compared to conventional SWL is the idea that SWs delivered from 2 sources may be able to break stones more efficiently than SWs from a single source. Others have presented in vitro data to suggest that this is the case.[5] In the current study we limited our analysis of stone breakage to the 2 conditions most relevant to the efficacy and safety of treatment involving 2 shock sources. Our in vitro results demonstrate that the number of delivered SWs and treatment time needed to achieve stone comminution were essentially similar under the alternating and simultaneous SW firing modes of dual head lithotripsy. With this in mind a possible benefit of dual pulse lithotripsy in alternating mode is that renal function was not significantly changed after treatment. This is in contrast to the renal vasoconstriction normally observed following simultaneous delivery of dual SWs[18] or SWs delivered from a conventional single head lithotriptor.[16,18]

CONCLUSIONS

Treatment of the pig kidney with a clinical dose of SWs delivered in alternating (asynchronous) mode with the Duet dual head lithotriptor caused minimal alteration in renal function and produced only a small hemorrhagic lesion. This demonstrates that the delivery of SWs from 2 treatment heads is not inherently dangerous and firing 2 SW sources at a combined rate of 240 SWs per minute does not cause significant morphological injury to the kidney.

ACKNOWLEDGMENTS

Cynthia D. Johnson and Philip M. Blomgren assisted with the study and Dr. James C. Williams, Jr. commented on the manuscript.

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