Renal Vasoconstriction Occurs Early During Shockwave Lithotripsy in Humans

Franklin C. Lee, MD,¹ Ryan S. Hsi, MD,¹ Mathew D. Sorensen, MD, MS,^{1,2} Marla Paun,³ Barbrina Dunmire,³ Ziyue Liu, PhD,⁴ Michael Bailey, PhD,³ and Jonathan D. Harper, MD¹

Abstract

Introduction: In animal models, pretreatment with low-energy shock waves and a pause decreased renal injury from shockwave lithotripsy (SWL). This is associated with an increase in perioperative renal resistive index (RI). A perioperative rise is not seen without the protective protocol, which suggests that renal vasoconstriction during SWL plays a role in protecting the kidney from injury. The purpose of our study was to investigate whether there is an increase in renal RI during SWL in humans.

Materials and Methods: Subjects were prospectively recruited from two hospitals. All subjects received an initial 250 shocks at low setting, followed by a 2-minute pause. Treatment power was then increased. Measurements of the renal RI were taken before start of procedure, at 250, after 750, after 1500 shocks, and at the end of the procedure. A linear mixed-effects model was used to compare RIs at the different time points.

Results: Fifteen patients were enrolled. Average treatment time was 46 ± 8 minutes. Average RI at pretreatment, after 250, after 750, after 1500 shocks, and post-treatment was 0.67 ± 0.06 , 0.69 ± 0.08 , 0.71 ± 0.07 , 0.73 ± 0.07 , and 0.74 ± 0.06 , respectively. In adjusted analyses, RI was significantly increased after 750 shocks compared with pretreatment ($p = 0.05$).

Conclusion: Renal RI increases early during SWL in humans with the protective protocol. Monitoring for a rise in RI during SWL is feasible and may provide real-time feedback as to when the kidney is protected.

Introduction

IN ANIMAL MODELS, adding low-energy shock waves, followed by a pause before a standard dose of high-energy shock waves, eliminated morphologic renal injury measured with the standard dose alone.^{1–10} This protection protocol was associated with a 14% increase in renal resistive index (RI) by the conclusion of the shockwave lithotripsy (SWL) treatment session that was not observed without the pause.^{7,8} Increased RI measured with ultrasound has often been used as an indicator of vasoconstriction, and it has been speculated that vasoconstriction during SWL has a protective effect.

Other protective techniques have been described.^{7–10} These include low-energy shock waves for about 4 minutes without the pause, slow shock delivery rate, or gradually ramping the shock wave pressure.^{8–10} Prior porcine studies have demonstrated that SWL-induced hemorrhagic renal injury can be reduced by more than 93%, from 5.2% to less than 0.4% functional renal volume, by instituting a renal protective protocol.^{1–5} This is presumed to be due to protective renal vasoconstriction; however, RI was not measured in these studies.

These protocols have been broadly adopted in clinical practice based on animal safety studies.¹¹ Despite increasing adoption of these protocols, there is no current evidence that demonstrates improved safety in humans with the use of these protocols. The purpose of this study was to determine if a renal protection protocol in humans treated with a modern lithotripter is associated with an intraoperative rise in renal RI, similar to what has been observed with the use of protection protocols in animals.

Materials and Methods

Seventeen patients were prospectively recruited from the University of Washington Medical Center and the Puget Sound Veterans Hospital after institutional review board approval from both sites. Inclusion criteria were age >18 years, a radio-opaque renal or ureteral stone, and plan to undergo SWL. Subjects were excluded if the interlobar renal arteries were unable to be imaged during treatment (two subjects). None of the patients received NSAIDs 7 days before their surgical procedure.

¹Department of Urology, University of Washington School of Medicine, Seattle, Washington.

²Division of Urology, Department of Veteran Affairs Medical Center, Seattle, Washington.

³Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, Washington.

⁴Department of Biostatistics, Indiana University Schools of Medicine and Public Health, Indianapolis, Indiana.

TABLE 1. PATIENT DEMOGRAPHICS

	Mean $\pm$ SD
Age	61 $\pm$ 15 years
Gender	
Male (%)	11 (73)
Female (%)	4 (27)
BMI	29 $\pm$ 5 kg/m ²
Stone laterality	
Right (%)	4 (27)
Left (%)	11 (73)
Average stone size	11 $\pm$ 8 mm
Mean number of stones treated per patient	1.5 $\pm$ 0.8
Mean operative time	46 $\pm$ 8 minutes

BMI = body-mass index; SD = standard deviation.

SWL was performed using the Dornier Compact Delta II lithotripter (16/17 patients, 94%) (Dornier MedTech, Munich, Germany) or Lithotron lithotripter (1/17 patients, 6%) (Healthtronics, Austin, TX) under fluoroscopic guidance. Patients were treated under general anesthesia in an outpatient setting. The specific protection protocol used here included a shockwave delivery rate of 60 shocks per minute. The initial 250 shocks were delivered at the lowest power setting, followed by a 2-minute pause in treatment. Treatment power was then incrementally increased for the remainder of the treatment. The rate at which the energy was increased and the total number of shocks delivered were at the surgeon's discretion.

The primary endpoint of this study was a rise in renal vascular RI. Doppler ultrasound (Siemens Acuson Sequoia 512; Siemens Medical solutions, Malvern, PA and HDI 5000; ATL/Philips Healthcare, Bothell, WA) was used to calculate RI from the peak systolic, V_S , and end-diastolic velocities, V_D , of an interlobar renal artery [$RI = (V_S - V_D)/V_S$]. A single experienced ultrasonographer in renal imaging performed each study and obtained each RI measurement. Following induction of general anesthesia and placement of the lithotripter head, a baseline RI was obtained before the start of SWL. The measurement was repeated after 250, 750, and 1500 shocks. Shock delivery was briefly paused for the RI measurement at each of the time points listed above. Time to measure RI was recorded. A final measurement was obtained at the end of the treatment before extubation and removal of the treatment head. Systolic and diastolic blood pressure at the time of each measurement was obtained from anesthesia records.

A linear mixed-effects model was used to compare RIs across different time points. All variables were entered into our model as categorical variables to account for potential non-linear effects. Age, gender, body-mass index (BMI), treatment side, and systolic and diastolic blood pressure were also included in this multiple variable model as covariates. A random intercept was adopted for each subject to handle within-subject correlations. Statistical significance was defined as $p < 0.05$. Analyses were performed using SAS (Cary, NC).

Results

Demographics and perioperative data

Seventeen patients underwent enrollment. Two patients were excluded due to the inability to measure RI intra-operatively. Fifteen subjects (4 female, 11 male) underwent SWL for renal calculi (11 left kidney, 4 right kidney). Fourteen patients underwent treatment with the Dornier Compact Delta II lithotripter, and one patient underwent treatment with the Lithotron lithotripter. Mean subject age was 61 $\pm$ 15 years, and average BMI was 29 $\pm$ 5 kg/m² (Table 1). Mean $\pm$ standard deviation stone size was 11 $\pm$ 8 mm, with five subjects (33%) undergoing treatment of multiple stones in different calices. Only one patient underwent concurrent ureteral stent, who had a total stone burden of 2.6 cm.

The mean operative time from the first to last shock was 46 $\pm$ 8 minutes (Table 1). Systolic and diastolic blood pressure decreased ($p < 0.001$) from induction to 250 shocks, and then increased slightly through the end of the treatment ($p = 0.19$ and $p = 0.79$, respectively) (Table 2).

Change in RI

Mean RIs at 250, 750, 1500 shocks, and post-treatment were all significantly higher than the pretreatment RI ($p < 0.001$) (Fig. 1). Overall, RI increased an average of 11% from pretreatment to post-treatment. On multivariate analysis, age, systolic blood pressure, gender, BMI, and side were not associated with the increase in RI. However, increased diastolic blood pressure was associated with a slight decrease in renal RI ($p = 0.02$). After adjusting for the covariates listed above, RI increased significantly beginning at 750 shocks ($p = 0.05$) when compared with pretreatment RI. Baseline RI did not appear to affect the significant rise in RI that was seen beginning at 750 shocks.

The initial measurement (pretreatment) of RI took the longest time to obtain with a mean of 153 $\pm$ 119 seconds. After this initial measurement, the time to measure renal vascular RI averaged 66 $\pm$ 48 seconds. In all cases, RI was

TABLE 2. RESISTIVE INDEX AND BLOOD PRESSURE DURING SHOCKWAVE LITHOTRIPSY

	RI	Increase in RI from pretreatment (%)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
Pretreatment	0.67 $\pm$ 0.06	—	123 $\pm$ 12	84 $\pm$ 8
250 shocks	0.69 $\pm$ 0.08	3	89 $\pm$ 8	56 $\pm$ 7
750 shocks	0.71 $\pm$ 0.07	7	93 $\pm$ 4	56 $\pm$ 5
1500 shocks	0.73 $\pm$ 0.08	9	97 $\pm$ 10	59 $\pm$ 10
Post-treatment	0.74 $\pm$ 0.06	11	115 $\pm$ 29	69 $\pm$ 16

mean $\pm$ SD.

RI = resistive index.

FIG. 1. Mean $\pm$ standard deviation of the resistive index as treatment progressed. Line is shown for ease of comprehension. Data were not obtained continuously.

measured in a single vessel even when treating multiple calices in the same pole of the kidney.

Discussion

Renal vascular RI has been shown in animal studies to play a role in renal protection during SWL in animal studies. In humans, renal RI has been implicated in disease states such as diabetes, hypertension, and renal artery stenosis. Prior studies have examined rises in RI immediately following SWL.^{12,13} These studies examined rises in RI as a predictor of long-term complications of SWL such as new onset diabetes and hypertension.^{14–18} As opposed to evaluating RI postoperatively, our study is the first to measure and demonstrate changes in RI intraoperatively in humans. We have found that RI increases significantly (11%) during the early period of SWL when using a protection protocol. These changes validate animal studies that have shown that intraoperative rises in RI are protective. Specifically, these animal studies found that a protection protocol is associated with a 14% increase in RI by the end of the SWL treatment session and a greater than 93% decrease in the volume of renal injury compared with SWL without this technique.^{7,8} These results suggest that protection protocols, commonly used in current practice, have the similar effect as that demonstrated in the porcine model.^{10,11,19} The mechanism by which RI increases during SWL is currently unknown. We theorize, however, that the energy from the shock waves causes a vascular spasm and vasoconstriction in small vessels, thereby increasing the effective RI. An increase in vascular resistance would reduce the renal blood flow leading to reduced hemorrhage and renal injury. In animal studies, we believe that the low-amplitude shocks and the pause allow renal vasculature time to constrict and vasospasm, resulting in an increase in RI compared with those without a pause.

The early increase in RI with a protection protocol appears to be a progressive, but nonlinear, phenomenon. We have found that rises in RI appear to occur rapidly within the first several 100 shocks, then plateau during treatment. We determined that the greatest change in RI occurred early in

treatment with small increases in RI occurring later. These data regarding the timing and increase of RI early during SWL add more specificity to the existing literature that reports an increase in RI in the postoperative setting. By encouraging vasoconstriction to occur early in treatment, the protective protocols may provide renal protection for a greater number of the shock waves delivered.

Low-amplitude shocks and a pause, slow shock delivery rate, and power ramping have all been shown to reduce injury in pigs treated with the Dornier HM3.^{5–9} In this study, we used a protocol that has been adopted at our institution that employs elements of all these techniques. Using modern lithotripters and human subjects, we demonstrated a rise in RI during treatment that is similar to that seen in animals. These data would support the use of these protocols that so many have adopted.

Renal vascular RI is obtained using ultrasonography and can be performed intraoperatively by a trained operator. While additional time and equipment are necessary to obtain measurements, overall, the additional time required was relatively short. We found that the pretreatment measurement of RI took the longest (153 ± 119 s), to initially locate the kidney and identify an appropriate interlobar artery. Once located, the time taken to obtain further measurements during active treatment was relatively short: 66 ± 48 seconds. Furthermore, our study suggests that the main rise in renal vascular RI occurs primarily in the beginning of the treatment, with a large rise by 250 shocks and relative stability of RI by 750 shocks.

There were several limitations to our study. Our sample size was small, thereby limiting our ability to generalize our results to a larger cohort. Our study did not include a control group exposed to SWL without a renal protective protocol as this raised ethical concerns about potentially creating more renal injury. The protective protocol included multiple interventions and thus determining which aspect might be most beneficial is not possible, although a consistent component of all the protocols is a delay to allow the kidney to respond before the delivery of higher-energy shock waves. Rises in RI appear to be multifactorial and complex. The exact role of blood pressure is unclear and the interaction with both diastolic and systolic blood pressure needs to be further studied. Our study did not measure RI postoperatively to see if results returned to baseline. Studies have suggested that chronic rises in RI following SWL may contribute to hypertension or diabetes; however, having said that, we believe that transient rises in RI are unlikely to have any significant long-term outcome. In addition, we did not directly or indirectly measure kidney injury, our sample size was relatively small, and there may have been additional confounders not controlled for in our analyses.

Conclusion

We believe that by monitoring intraoperative renal vascular RI, this measure can be utilized to determine when a kidney is protected and guide treatment. While at the moment this does require the use of a trained ultrasonographer and additional equipment, further technological advancements may make this technology a feasible way to allow surgeons to more efficiently ramp-up treatment power once renal vascular RI has been shown to be elevated and the kidney protected. This could lead to shorter operative times and more effective shock wave delivery.

Acknowledgments

The authors thank their colleagues at the Consortium for Shock Waves in Medicine and the Center for Medical and Industrial Ultrasound. This work was supported by NIH NIDDK grants, DK043881 and DK092197, and the National Space Biomedical Research Institute through NASA NCC 9-58. This material is the result of the work supported by resources from the VA Puget Sound Healthcare System, Seattle, Washington.

Author Disclosure Statement

No competing financial interests exist.

References

1. Delius M, Enders G, Xuan ZR, Liebich HG, Brendel W. Biological effects of shock waves: Kidney damage by shock waves in dogs—dose dependence. *Ultrasound Med Biol* 1988;14:117–122.
2. Delius M, Jordan M, Eizenhoefer H, et al. Biological effects of shock waves: Kidney haemorrhage by shock waves in dogs—administration rate dependence. *Ultrasound Med Biol* 1988;14:689–694.
3. Connors BA, Evan AP, Blomgren PM, et al. Reducing shock number dramatically decreases lesion size in a juvenile kidney model. *J Endourol* 2006;20:607–611.
4. Kaude JV, Williams CM, Millner MR, Scott KN, Finlayson B. Renal morphology and function immediately after extracorporeal shock-wave lithotripsy. *AJR Am J Roentgenol* 1985;145:305–313.
5. Willis LR, Evan AP, Connors BA, Blomgren P, Fineberg NS, Lingeman JE. Relationship between kidney size, renal injury, and renal impairment induced by shock wave lithotripsy. *J Am Soc Nephrol* 1999;10:1753–1762.
6. Connors BA, Evan AP, Willis LR, Blomgren PM, Lingeman JE, Fineberg NS. The effect of discharge voltage on renal injury and impairment caused by lithotripsy in the pig. *J Am Soc Nephrol* 2000;11:310–318.
7. Handa RK, McAteer JA, Connors BA, et al. Optimising an escalating shockwave amplitude treatment strategy to protect the kidney from injury during shockwave lithotripsy. *BJU Int* 2012;110:E1041–1047.
8. Handa RK, Bailey MR, Paun M, et al. Pretreatment with low-energy shock waves induces renal vasoconstriction during standard shock wave lithotripsy (SWL): A treatment protocol known to reduce SWL-induced renal injury. *BJU Int* 2009;103:1270–1274.
9. Connors BA, Evan AP, Blomgren PM, et al. Extracorporeal shock wave lithotripsy at 60 shock waves/min reduces renal injury in a porcine model. *BJU Int* 2009;104:1004–1008.
10. Willis LR, Evan AP, Connors BA, et al. Prevention of lithotripsy-induced renal injury by pretreating kidneys with low-energy shock waves. *J Am Soc Nephrol* 2006;17:663–673.
11. Brown RD, De S, Sarkissian C, Monga M. Best practices in shock wave lithotripsy: A comparison of regional practice patterns. *Urology* 83:1060–1064.
12. Aoki Y, Ishitoya S, Okubo K, et al. Changes in resistive index following extracorporeal shock wave lithotripsy. *Int J Urol* 1999;6:483–492.
13. Mohseni MG, Khazaeli H, Aqhamir S, et al. Changes in intrarenal resistive index following electromagnetic extracorporeal shock wave lithotripsy. *Urol J* 2007;4:217–220.
14. McAteer JA, Evan AP. The acute and long-term adverse effects of shock wave lithotripsy. *Semin Nephrol* 2008;28:200–213.
15. Morris JS, Husmann DA, Wilson WT, Preminger GM. Temporal effects of shock wave lithotripsy. *J Urol* 1991;145:881–883.
16. Janetschek G, Frauscher F, Knapp R, Hofle G, Peschel R, Bartsch G. New onset hypertension after extracorporeal shock wave lithotripsy: Age related incidence and prediction by intrarenal resistive index. *J Urol* 1997;158:346–351.
17. Knapp R, Frauscher F, Helweg G, Judmaier W, Strasser H, Bartsch G, zur Nedden D. Blood pressure changes after extracorporeal shock wave nephrolithotripsy: Prediction by intrarenal resistive index. *Eur Radiol* 1996;6:665–669.
18. Williams CM, Kaude JV, Newman RC, Peterson JC, Thomas WC. Extracorporeal shock-wave lithotripsy: Long-term complications. *AJR Am J Roentgenol* 1988;150:311–315.
19. Coe FL. *Kidney stones: Medical and surgical management*. Philadelphia: Lippincott-Raven, 1996.

Address correspondence to:

Franklin C. Lee, MD

Department of Urology

University of Washington School of Medicine

1959 NE Pacific Street

Box 356510

Seattle, WA 98195

E-mail: franklee@uw.edu

Abbreviations Used

BMI = body-mass index

RI = resistive index

SWL = shockwave lithotripsy