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*IEEE Int Ultrason Symp.* 2014 September 3; 2014: 1013–1016. doi:10.1109/ULTSYM.2014.0248.**Shockwave lithotripsy with renoprotective pause is associated with renovascular vasoconstriction in humans****Michael Bailey<sup>1</sup>, Franklin Lee<sup>2</sup>, Ryan Hsi<sup>2</sup>, Marla Paun<sup>1</sup>, Barbrina Dunmire<sup>1</sup>, Ziyue Liu<sup>3</sup>, Mathew Sorensen<sup>2,4</sup>, and Jonathan Harper<sup>2</sup>**Michael Bailey: [bailey@apl.washington.edu](mailto:bailey@apl.washington.edu)<sup>1</sup>Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, USA<sup>2</sup>Department of Urology, University of Washington, Seattle, USA<sup>3</sup>Department of Biostatistics, Indiana University School of Medicine, Indianapolis, USA<sup>4</sup>Division of Urology, Puget Sound Veteran Affairs Medical Center, Seattle, USA**Abstract**

Animal studies have shown that shock wave lithotripsy (SWL) delivered with an initial course of low-energy shocks followed by a pause reduces renal injury. The pause correlates with increased arterial resistive index (RI) during SWL as measured by ultrasound. This suggests that renal vasoconstriction is associated with protecting the kidney from injury. This study explored whether a similar increase in RI is observed in humans. Patients were prospectively recruited from two hospitals. All received an initial dose of 250 lowest energy shocks followed by a two-minute pause. Shock power was then ramped up at the discretion of the physician; shock rate was maintained at 1 Hz. Spectral Doppler velocity measurements were taken from an interlobar artery at baseline after induction, during the pause at 250 shocks, after 750 shocks, after 1500 shocks, and at the end of the procedure. RI was calculated from the peak systolic and end diastolic velocities and a linear mixed-effects model was used to compare RIs. The statistical model accounted for age, gender, laterality, and body mass index (BMI). Measurements were taken from 15 patients. Average RI  $\pm$  standard deviation pretreatment, after 250 shocks, after 750 shocks, after 1500 shocks, and post treatment was  $0.68 \pm 0.06$ ,  $0.71 \pm 0.07$ ,  $0.73 \pm 0.06$ ,  $0.75 \pm 0.07$  and  $0.75 \pm 0.06$ , respectively. RI was found to be significantly higher after 250 shocks compared to pretreatment ( $p = 0.04$ ). RI did not correlate with age, gender, BMI, or treatment side. This is suggestive that allowing a pause for renal vascular vasoconstriction to develop may be beneficial, and can be monitored for during SWL, providing real-time feedback as to when the kidney is protected.

**Keywords**

resistive index; vasoconstriction; ultrasound; shock wave lithotripsy

**I. Introduction**

There are approximately 350,000 shock wave lithotripsy (SWL) procedures performed annually in the U.S. - the most common surgical treatment for nephrolithiasis [1]. SWL is

transcutaneous, minimally invasive, and generally safe. Although complications related to the procedure are uncommon, there is a component of acute kidney injury that occurs as a result of the high energy shocks. The extent of injury in humans is unknown. The extent of acute renal injury in animals though has been evaluated histologically and found to be as high as 7.6% of the functional renal volume. The extent of injury was found to be dependent on the number of shock waves administered, the pulse amplitude, and the rate of shockwave delivery [2–10].

Research in animals focused on reducing shock wave-induced injury determined that the loss of functional volume can be reduced by minimizing the total number of shock waves, maintaining a shock wave rate of 60 shocks per minute, and slowly increasing the power amplitude of the shock waves [11,12]. In particular, initiating treatment with low energy shock waves and a pause was shown to eliminate injury in pigs, and has been termed the “protection protocol” [5,12,13]. The protection protocol has also been shown to be associated with an increase in (pig) renal vascular resistive index (RI) intraoperatively, which is not seen in kidneys without the pretreatment [5,14]. Human and pig kidneys have been shown to be in a state of vasoconstriction after SWL; only with the protection protocol has the RI been shown to have a significant rise during SWL. The supposition is thus that vasoconstriction induced by the protocol protects the kidney from injury while the shock waves are applied.

Many clinicians have adopted the use of the protection protocol based on the results of the animal studies. Yet there are no studies indicating whether the protocol has a benefit in humans, or if a change in RI occurs. Our study seeks to evaluate if renal vascular RI increases in humans similarly to what has been observed in animal studies.

## II. Materials and Methods

### A. Study Population

Seventeen patients were prospectively recruited from the University of Washington Medical Center and the Puget Sound Veterans Hospital. Inclusion criteria were age > 18 years, a radio-opaque renal or ureteral stone planning to undergo SWL. Subjects were excluded if we were not able to adequately image the kidney or renal vessel during treatment.

### B. Study Protocol

SWL was performed using the Dornier Compact Delta II Lithotripter (Dornier MedTech, Munich, Germany) or Lithotron (Healthtronics, Austin TX, USA) with fluoroscopic guidance. Patients were treated under general anesthesia at a rate of 60 shocks per minute for a minimum of 1500 shocks and a maximum of 2500 shocks. The initial 250 shocks were delivered at the lowest power setting and all patients had a two minute pause in treatment following delivery of 250 shocks. Treatment power was incrementally increased for the remainder of the treatment. The manner in which the power was increased and the total number of shocks delivered was at the surgeon’s discretion. The study and protocol was approved by the institutional review board of both institutions included in this study.

RI was calculated from peak systolic and end diastolic velocities measured using Doppler ultrasound (Siemens Acuson Sequoia 512, Siemens Medical solutions, Malvern, PA and HDI 5000, Phillips, Amsterdam, Netherlands). All measurements were taken from the same interlobar renal artery by a sonographer trained in renal imaging. Treatment was briefly paused for the measurement. The length of treatment delay was recorded as well as the systolic and diastolic blood pressure (from the anesthesia records). Baseline velocity measurements were taken prior to the start of SWL, but after induction of general anesthesia and coupling of the lithotripter. Subjects were excluded if an adequate baseline RI could not be obtained. The velocity measurements were repeated after 250 shocks, 750 shocks, 1500 shocks, and at the completion of the study, prior to extubation and decoupling of the lithotripter.

### C. Statistical Model

A linear mixed effects model was used to compare RI across different time points with statistical significance defined as  $p < 0.05$ . A random intercept was adopted for each subject to handle within-subject correlations. Time was included as a categorical variable to account for potential nonlinear effects. The same model was used to control for age, gender, BMI, side, and intraoperative blood pressure.

## III. Results

RI data was collected from fifteen subjects undergoing SWL for renal calculi. This included 4 female and 11 male subjects, 11 left kidney stones and 4 right kidney stones. Two patients were excluded due to an inability to obtain baseline RI. Mean subject age was  $61 \pm 15$  and average BMI was  $29 \pm 5$  (Table 1). Average stone size was  $11 \pm 8$  mm, with 5 subjects (33%) undergoing treatment of multiple stones in different calyces.

### A. Perioperative

Mean operative time from induction of anesthesia to extubation was  $82 \pm 12$  minutes with an average procedure time of  $46 \pm 8$  minutes. Mean blood pressure dropped significantly ( $p < 0.001$ ) within the first 250 shocks and showed a consistent, but non-significant increase, from 250 shocks to the end of treatment ( $p = 0.19$  systolic,  $p = 0.79$  diastolic) (Table 1).

### B. Resistive Index

Mean RI rose to a significantly higher level than baseline after delivery of 250 shocks ( $p = 0.04$ ) (Table 1) and remained elevated through 750 shocks, 1500 shocks, and post-treatment (each  $p < 0.001$  relative to pre-treatment). There was no significant change in RI after administration of 750 shocks ( $p = 0.18$ ), though there was a slight increase in RI throughout the procedure (Figures 1 and 2). Treatment delay to measure renal vascular RI was on average  $66 \pm 48$  seconds.

On multivariate analysis age, systolic blood pressure, gender, BMI, and renal side were not associated with increases in RI. A lower diastolic blood pressure was associated with a higher RI ( $p=0.02$ ). After adjusting for both systolic and diastolic blood pressure, RI became significantly higher than pre-treatment RI beginning at 750 ( $p = 0.05$ ) versus 250 shocks.

## IV. Discussion

SWL is associated with renal injury. Porcine kidney studies have shown this is primarily due to the rupture of blood vessels. As an example, standard treatment using a Dornier HM3 lithotripter delivering 2000 shocks at 120 SW/minute and 24 kV has been shown to result in a 5–6% loss of functional renal volume [13]. In humans, the amount of injury due to SWL treatment is unknown, though some investigators believe that repeated treatment may lead to renal fibrosis and long-term medical complications.

Investigators studying the effects of post-SWL complications have utilized multiple clinical parameters including excretory urography, computed tomography, magnetic resonance imaging, radionuclide renography, and renal vascular RI. RI has proven sensitive for vascular and tubulointerstitial diseases of the kidney in other clinical settings, with values greater than 0.7 often indicative of pathology. Studies evaluating the correlation between SWL treatment and renal vascular RI have demonstrated that the majority of patients show a significant rise in RI as early as 30 minutes post-treatment, and, in some cases, RI may remain elevated for months following treatment [12–14]. While the clinical implications of a transient rise in renal vascular RI are unclear, a long-term and persistent rise in RI has been implicated in new onset hypertension, particularly for the elderly [15–17]. Knapp et al. (1996) found that an RI value surpassing 0.69 was 80% sensitive and 80% specific in predicting arterial hypertension in patients who underwent ESWL treatment [17].

These studies suggest that a persistent elevated renal vascular RI post treatment, which is indicative of vasoconstriction and decreased renal perfusion, may be associated with renal injury. In contrast, animal studies have suggested that an elevated intraoperative RI may be renal protective. Results showed that kidneys exposed to a renal-protective protocol had reduced functional renal injury (as a result of SWL) by as much as 85% [5,12,13]. Renal protection was achieved by an initial administration of four minutes of either low dose energy shocks or low dose shocks combined with a treatment pause. In the animal studies, both protocols were associated with a significant rise in intraoperative renal RI. Kidneys not exposed to this renal-protective protocol showed no changes in renal vascular RI during treatment or reduction in functional injury. The authors hypothesized that the intraoperative rise in renal vascular RI resulted in decreased effective blood flow to the kidney, leading to a reduction in hemorrhage and subsequent decrease in overall renal injury. It is important to note that all kidneys treated, regardless of whether they underwent a renal-protective protocol or not, had significantly higher post-treatment renal vascular RI compared to pre-treatment.

Our results in human subjects using a renal-protective SWL protocol show a similar response in RI as in the animal studies [5,11–14]. Based on our findings, we believe that an elevated renal vascular RI is not solely an indication of renal injury, as is suggested by the current literature [15–17]. We believe that an increase in RI early during treatment is indicative of a “protected” state, while sustained elevations of RI following treatment may predict renal scarring and long-term complications.

Renal vascular RI is measured with ultrasound and can be performed during SWL treatment by a trained specialist. Overall, the additional time required was minimal. We found that the pre-treatment measurement of RI took the longest ( $153 \pm 119$  seconds), presumably to initially locate the kidney and identify an appropriate interlobar artery. Once located, time taken to obtain further measurements during active treatment was only  $66 \pm 48$  seconds. Furthermore, our study suggests that the main rise renal vascular RI occurs primarily in the beginning of treatment, with a large rise by 250 shocks and relative stability of RI by 750 shocks.

There are limitations to our study. First, we lacked a control group where subjects are exposed to SWL without a renal-protective protocol. Animal studies have shown this is associated with increased renal injury, which raises ethical concerns. We were also unable to obtain renal vascular RI without briefly stopping treatment – i.e. we would introduce a pause even in the control group. Our sample size was relatively small and we were unable to control for comorbid conditions and medications. Lastly, while we were able to control for systemic blood pressure changes, there may have been an additional relationship between systemic blood pressure and renal RI that was not controlled for in the included analyses.

## V. Conclusion

This paper reports on the first study to demonstrate the effect of a renal protective protocol during SWL on intraoperative RI in humans. We found that the increase in renal vascular RI parallels animal studies that have demonstrated that an increase in RI during treatment is associated with decreased histologic renal injury. Our data support prior research suggesting a delay in increasing shock wave energy until after four minutes of pretreatment (with low-energy shock waves or a brief pause) is sufficient to achieve the renal protection. The use of intraoperative monitoring of renal vascular RI may be a valuable tool; we believe that this measure can be utilized to determine when a kidney is “protected” and guide treatment. Further research is needed to determine the exact role of renal vascular RI in both immediate and long-term complications.

## Acknowledgments

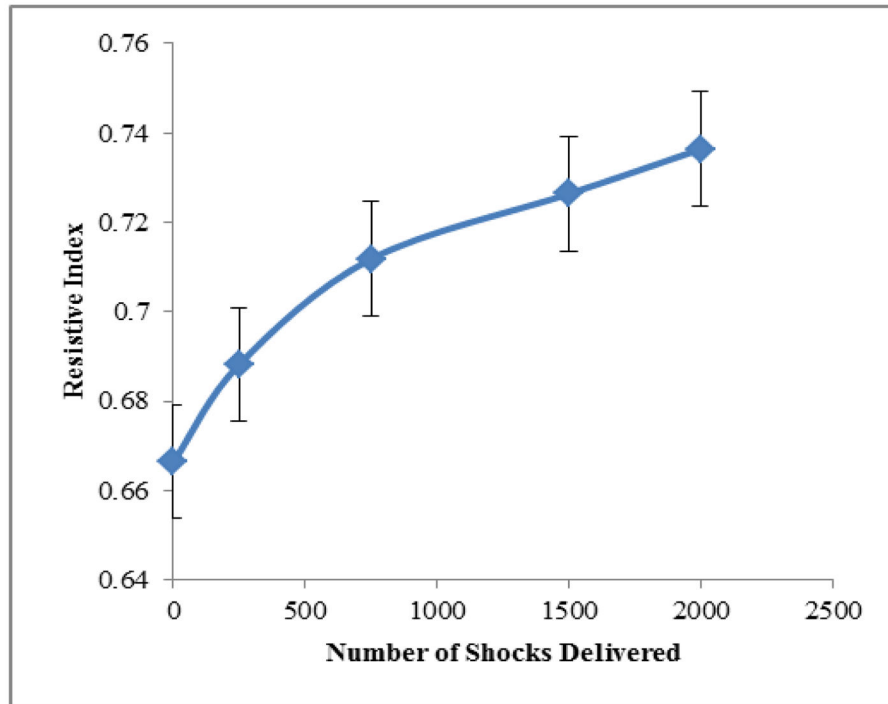
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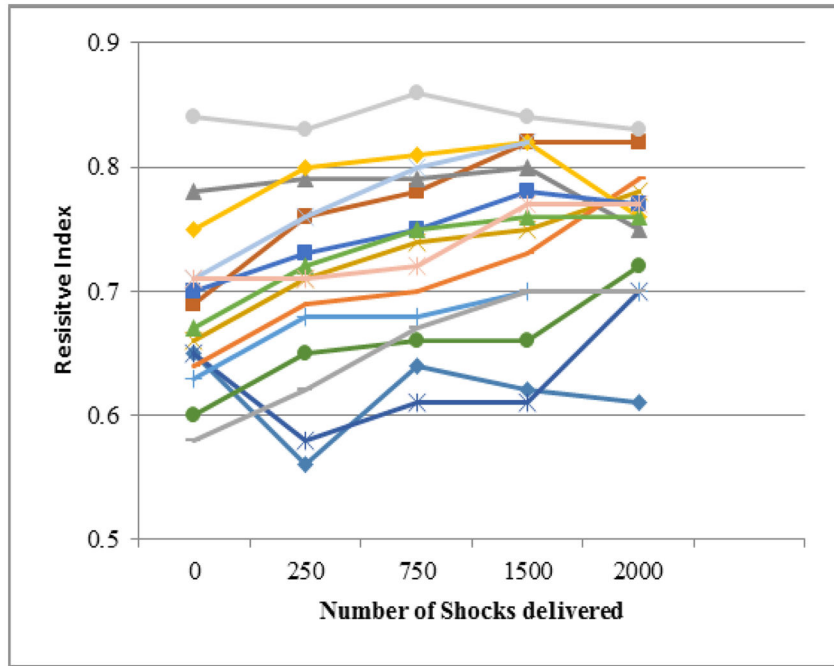
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**Figure 1.** Average RI index measured during the treatment procedure. Error bars represent standard deviation.



**Figure 2.**  
Individual RI index measurements for all 15 subjects.



**TABLE I**

Resistive Index (RI) and Blood Pressure Results during ESWL

Treatment Time	RI*	Systolic Blood Pressure* (mmHg)	Diastolic Blood Pressure* (mmHg)
Pre-treatment	0.66 ± 0.06	123 ± 12	84 ± 8
250 Shocks	0.69 ± 0.08	89 ± 8	56 ± 7
750 Shocks	0.72 ± 0.07	93 ± 4	56 ± 5
1500 Shocks	0.73 ± 0.07	97 ± 10	59 ± 10
Post-Treatment	0.74 ± 0.06	115 ± 29	69 ± 16

\* Mean +/- standard deviation

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