

# Prevention of Lithotripsy-Induced Renal Injury by Pretreating Kidneys with Low-Energy Shock Waves

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Lithotripsy shock waves (SW) to one renal pole damage that pole but protect the opposite pole from the damage inflicted by another, immediate application of SW. This study investigated whether the protection (1) occurs when the first treatment causes no injury, (2) is caused by SW or injury, (3) exhibits a threshold, and (4) occurs when the same pole receives both treatments. Six- to 7-wk-old anesthetized female pigs were studied. The following groups were studied: group 1 ( $n = 4$ ), 2000 SW at 12 kV to one pole and 2000 SW at 24 kV (standard) to the opposite pole; group 2 ( $n = 6$ ), same as group 1 except 500 12-kV SW pretreatment; group 3 ( $n = 8$ ), 500 12-kV, 2000 standard SW, all to the same pole; and group 4 ( $n = 8$ ), same as group 3 except 100 12-kV SW pretreatment. Mean  $\pm$  SD lesion size in group 1, first pole treated, was  $0.66 \pm 0.82\%$  of functional renal volume (FRV;  $P < 0.05$  versus  $5.22 \pm 3.6\%$  FRV with no pretreatment [NP]; 95% confidence interval [CI]  $-7.0$  to  $-2.1$ ) and  $0.50 \pm 0.68\%$  FRV in the opposite pole after 2000 standard SW ( $P < 0.05$  versus NP; 95% CI  $-9.4$  to  $-0.08$ ). Mean lesion size (first pole) in group 2 was  $0.020 \pm 0.028\%$  FRV ( $P < 0.01$  versus NP; 95% CI  $-9.2$  to  $-1.2$ ) and  $0.43 \pm 0.54\%$  FRV in the opposite pole after 2000 standard SW ( $P < 0.05$  versus NP; 95% CI  $-8.8$  to  $-0.82$ ). Same-pole SW (groups 3 and 4) also protected. Mean lesion sizes were  $0.28 \pm 0.33\%$  ( $P < 0.01$  versus NP; 95% CI  $-8.0$  to  $-1.9$ ) in group 3 and  $0.39 \pm 0.48\%$  FRV ( $P < 0.01$  versus NP; 95% CI  $-8.2$  to  $-1.7$ ) in group 4. It is concluded that the pretreatment protocol substantially limits the renal injury that normally is caused by SWL and occurs when the pretreatment and standard SW are applied to the same pole. The threshold for the protection may be  $<100$  SW.

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Shock wave lithotripsy (SWL) remains the principal treatment for symptomatic renal calculi despite increasing awareness that SW damage the renal parenchyma (1–5). Clinical interest in treatment strategies aimed at minimizing the renal damage is high, and manufacturers of second- and third-generation lithotripters have produced machines with higher power and smaller focal zones, ostensibly to enhance stone comminution and diminish injury to renal tissue. Ironically, this combination seems actually to have exacerbated the problem of renal injury caused by SW. The incidence of perirenal hematomas in patients who were treated with the first-generation unmodified Dornier HM3 lithotripter, for example, has been reported consistently as  $<1\%$  (6,7), whereas that for such second-generation lithotripters as the Storz Modulith and Dornier Doli-S have been reported as 4.1 (8) and 12% (9), respectively.

This article reports a treatment strategy, devised in a porcine model, in which the renal damage that is caused by a clinical dose of SW that is applied with the unmodified Dornier HM3

lithotripter can be minimized or, possibly, prevented. The strategy derives from our initial observation (10) that the application of 2000 SW at 24 kV to one renal pole (upper or lower), which normally produces a hemorrhagic lesion amounting to nearly 7% of the functional renal volume (FRV) (5), caused substantially less injury in the opposite pole (lesion size was 0.1% FRV) when 2000 SW (also at 24 kV) were applied immediately to that pole (Figure 1).

The studies described in this article aimed at confirming and characterizing this protective response and asked whether (1) the response occurred after pretreatment with low-energy SW, which cause minimal detectable damage to the renal parenchyma; (2) the response was initiated by tissue injury or by the SW independent of injury; (3) a minimum, or threshold, exists for the number of SW needed to initiate the protective response; and (4) the protection occurs when the pretreatment and standard SW are applied to the same renal pole.

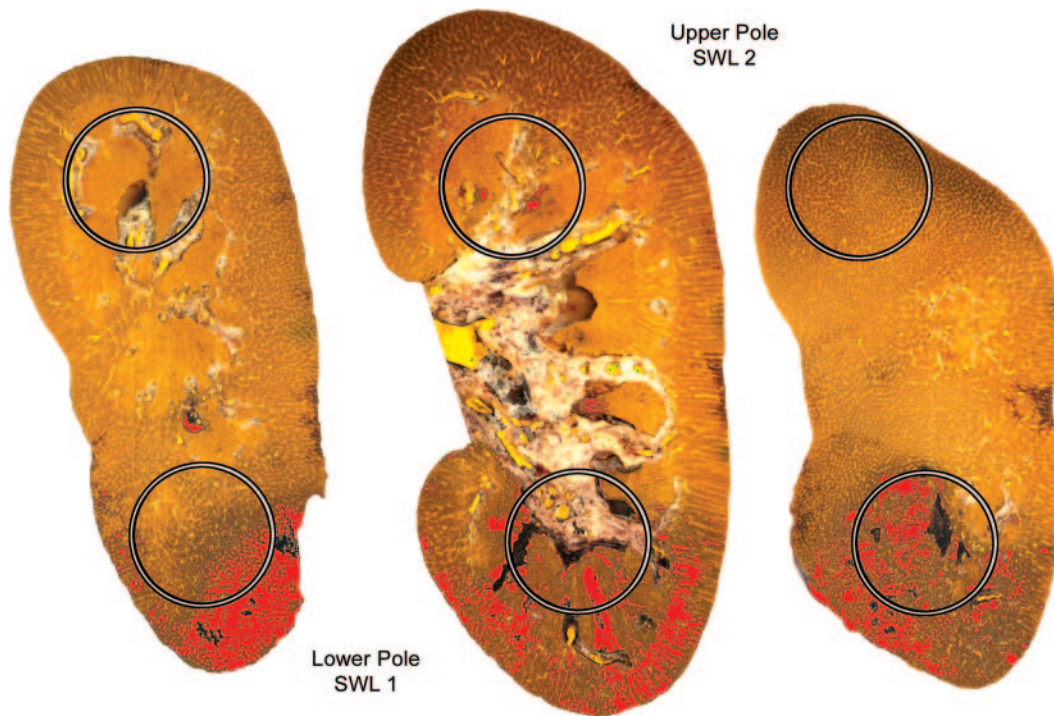
## Materials and Methods

The experimental protocol used in this study was carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and was approved by the Institutional Animal Care and Use Committees of the Indiana University School of Medicine and Methodist Hospital. Female farm pigs, 6 to 7 wk of age (Hardin Farms, Danville, IN), were randomly assigned to one of the following treatment groups. Group 1 ( $n = 4$ ) received 2000 SW at 12 kV to one renal pole (upper or lower) and 2000 SW at 24 kV to the opposite

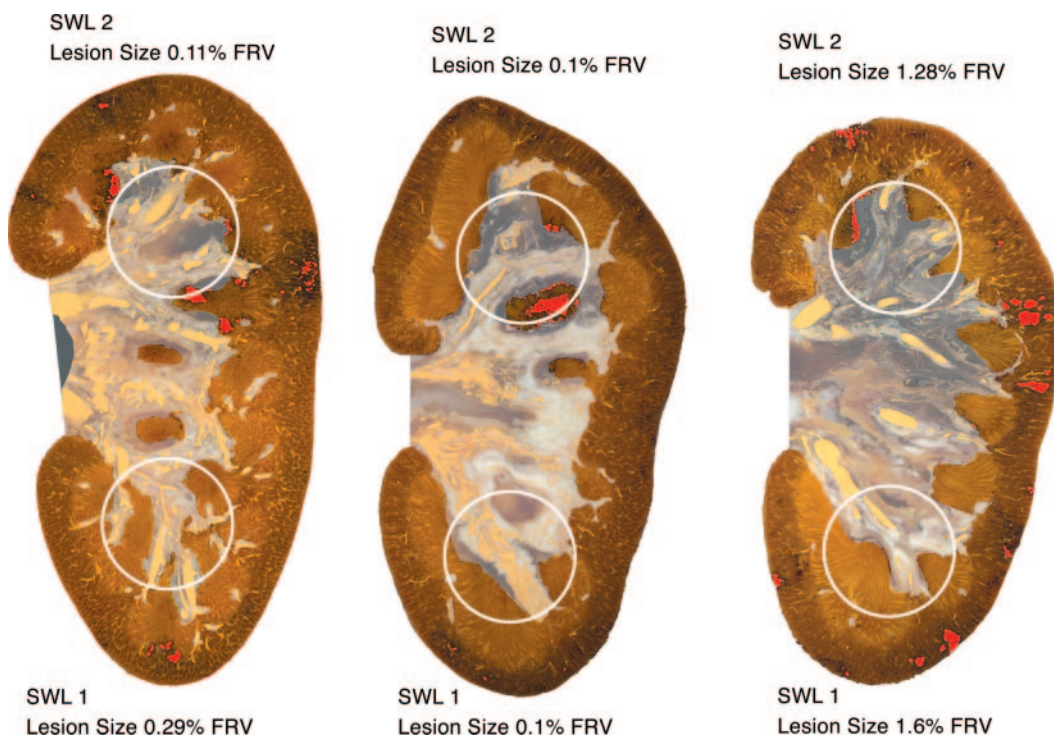
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*Figure 1.* Digitized serial-section images (coronal plane) of a kidney that had been treated first with 2000 shock waves (SW) at 24 kV to the lower pole (shock wave lithotripsy [SWL] 1) and immediately thereafter with the same “dose” (2000 SW at 24 kV) to the opposite pole (SWL 2). The circles denote the focal zone (F2) of the SW. Hemorrhagic lesions that were identified in the parenchyma are shown in red. The lesion in the lower pole composed 6.8% of the functional renal volume (FRV), whereas that in the upper pole was barely detectable (0.1% FRV).



*Figure 2.* Digitized images (mid-coronal plane) of three kidneys from group 1. One pole of each kidney was pretreated with 2000 SW at 12 kV (SWL 1). The opposite pole then was treated immediately with a standard clinical “dose” of SW (2000 at 24 kV). The circles denote F2 for each treatment. Hemorrhagic lesions are shown in red; cumulative lesion sizes that were measured in each pole are shown as % FRV.

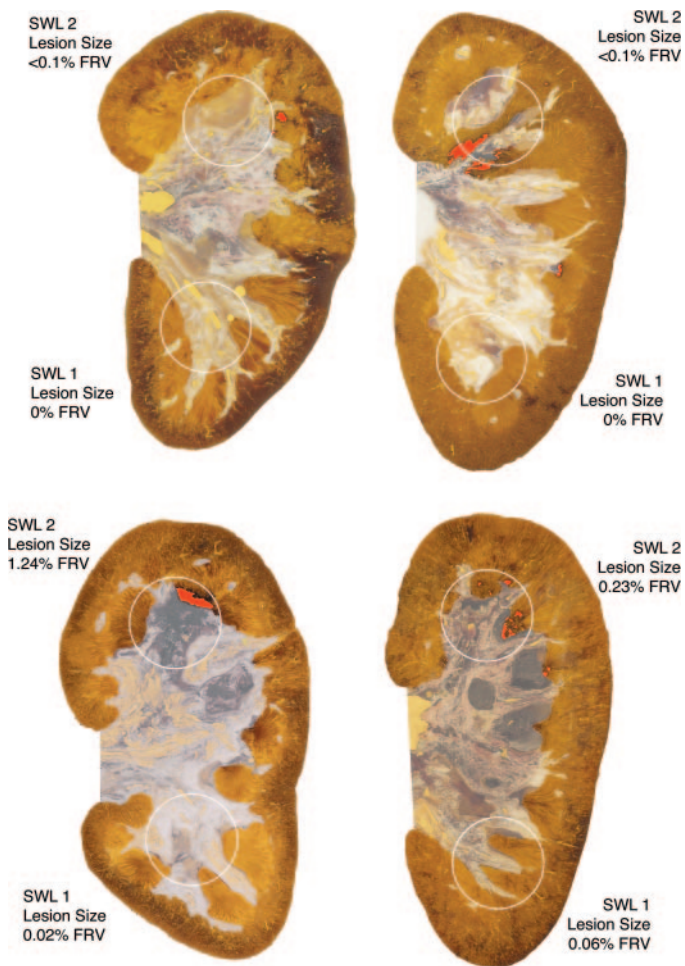


Figure 3. Digitized images (mid-coronal plane) of four kidneys from group 2. One pole of each kidney was pretreated with 500 SW at 12 kV (SWL 1). The opposite pole then was treated immediately with a standard clinical “dose” of SW (2000 at 24 kV). The circles denote F2 for each treatment. Hemorrhagic lesions are shown in red; cumulative lesion sizes that were measured in each pole are shown as % FRV.

pole of the same kidney. The rationale for this treatment strategy stems from our earlier observation (11) that renal tissue that was treated with 2000 SW at low activation energy (12 kV) sustained little to no injury. The pigs of group 2 ( $n = 6$ ) were treated in the identical manner as those of group 1 except that the initial treatment consisted of 500 SW at 12 kV. Group 3 ( $n = 8$ ) received 500 SW at 12 kV to one renal pole (upper or lower) and 2000 SW at 24 kV to the *same* pole of the same kidney. Group 4 ( $n = 8$ ) was treated in the identical manner as group 3 except that the pretreatment consisted of 100 SW at 12 kV. SW were applied only to one kidney in each animal, albeit twice in each experiment.

On the day of the experiment, each pig was anesthetized (15 to 20 mg/kg ketamine and 2 mg/kg xylazine for induction and intubation and 1 to 3% isoflurane and 100% oxygen for maintenance) and prepared for renal clearance experiments. Respiration was spontaneous. Surgical procedures for placement of arterial, renal venous, and bilateral ureteral catheters have been described previously (5). Isotonic saline was infused intravenously at 1 to 3% of body weight during the 90 min preceding the start of sample collection to maintain adequate hydration and urine flow.

Polyfructosan, 5% (Inutest; Henstettler, Linz, Austria), and sodium para-aminohippurate (PAH), 10%, were infused intravenously in isotonic saline at 1 ml/min to attain steady-state concentrations. At 45 min into the infusion, three consecutive 15-min baseline collections of urine were obtained from each kidney. Femoral arterial and bilateral renal venous blood samples were drawn at the midpoint of each collection period. At the conclusion of the third collection, the pigs were disconnected from the anesthesia machine and transferred (unconscious) to the lithotripsy suite (a trip of approximately 5 min), where administration of isoflurane anesthesia was resumed and preparations for SWL (unmodified Dornier HM3) were made. F2 was targeted on the lower pole calyx of the right or left kidney with the aid of fluoroscopy, and a small amount of contrast medium was injected through the ureteral catheter. SW then were delivered to that calyx at a rate of 2 impulses per second according to one of the protocols described above (only one kidney in each animal received SWL). An interval of 3 min duration elapsed after the application of the 12-kV SW, during which F2 was retargeted and 2000 SW were applied at 24 kV to the opposite pole of that kidney (groups 1 and 2) or to the same site that had received the low-energy SW (groups 3 and 4). The electrode was changed during the 3-min interval. At the end of the lithotripsy treatment, the pigs were

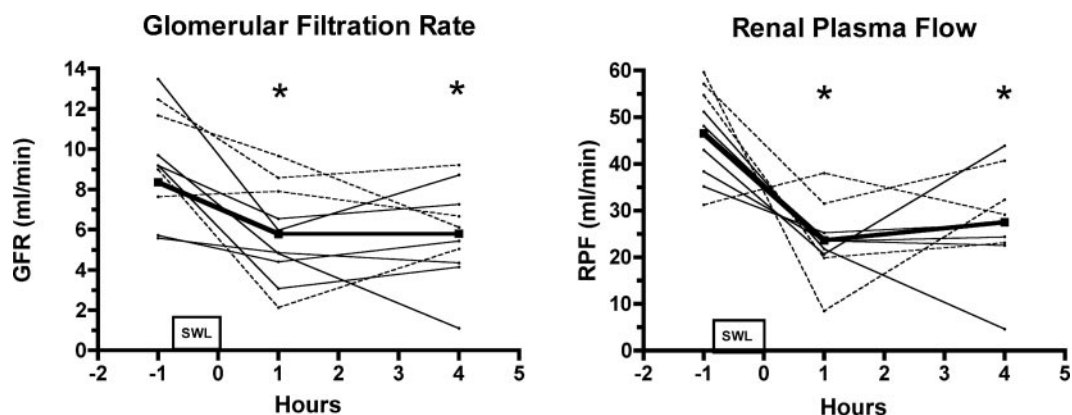


Figure 4. Renal hemodynamics measured in groups 1 (dashed lines) and 2 (light solid lines) before and at 1 and 4 h after the protection protocol (low-energy SW to one renal pole; standard clinical SW to the opposite pole) had been applied (see Materials and Methods for details). The dashed and light solid lines show data from individual pigs; the heavy solid lines denote mean data for the combined groups. \* $P < 0.01$  versus baseline for *post hoc* comparisons. See Results and Table 1 for details of analysis.

removed immediately from the water bath and returned to the surgical suite for three 15-min urine collections with midpoint blood samples at 1 and 4 h after SWL. The kidneys then were perfusion-fixed *in situ* (5) and removed for routine or quantitative morphologic analysis (12).

Lesion sizes were determined in the shocked kidneys from three of four kidneys in group 1, four of six kidneys in group 2, six of eight kidneys in group 3, and five of eight kidneys in group 4 (kidneys not used for determination of lesion size were used for routine histology). Lesion size was determined as a fraction of functional renal volume (FRV) for each whole kidney after serial sections (120  $\mu\text{m}$ ) that were digitally photographed for computer-assisted segmentation were obtained. The hemorrhagic regions were identified and colorized (13). Kidneys that were used for quantifying lesion size could not be used also for routine histology because different tissue preparation methods are required for each process. Consequently, the kidneys that were used for routine histology were embedded in paraffin, sectioned at 7  $\mu\text{m}$ , and stained with hematoxylin and eosin.

Urine and plasma samples were analyzed by standard colorimetric methods (14,15). Clearances of polyfructosan and PAH were calculated as estimates, respectively, of GFR and renal plasma flow (RPF). The concentration of PAH in renal venous blood was used to calculate the renal extraction of PAH, which provides an index of renal tubular secretory function. The clearance data were analyzed by one-way repeated-measures ANOVA. When the F test was statistically significant, the Newman-Keuls test and group *t* test were used where appropriate. Mean data are presented  $\pm$  SD and 95% confidence intervals (CI) for differences.  $P < 0.05$  was the criterion for statistical significance.

## Results

Figure 2 shows digitized and colorized cross-sections of the three kidneys from group 1. The first dose of 2000 SW was administered to the pigs of this group at an activation energy (12 kV) that normally causes minimal injury to renal tissue (11). Accordingly, the mean size of the lesions that were produced after the pretreatment in these pigs was  $0.66 \pm 0.82\%$  of FRV (individual lesion sizes are provided in Figure 2). Had the second dose of 2000 SW at 24 kV been applied to kidneys without any pretreatment, hemorrhagic lesions that are similar in size to what we normally observe after application of a single dose of 2000 SW at 24 kV to one renal pole would have been expected. The mean size of such lesions (*i.e.*, those in unprotected kidneys) that have been measured to date in our laboratory is  $5.22 \pm 3.61\%$  of FRV ( $n = 12$  kidneys). By comparison, the second application of SW to the pretreated kidney of group 1 produced lesions that were, on average, only approximately 10% as large as lesions that were produced in the absence of the low-energy treatment ( $0.50 \pm 0.68\%$  of FRV;  $P < 0.05$ ; 95% CI  $-0.94$  to  $-0.08$ ).

Figure 3 shows digitized and colorized cross-sections of the four kidneys from group 2. This experiment asked whether the protective response could be initiated by a smaller number of low-energy SW (500) applied to the pole opposite that to which the higher energy SW were applied. The initial treatment with 500 low-energy SW produced small lesions that composed, on average,  $0.020 \pm 0.028\%$  of FRV. The subsequent application of 2000 SW at 24 kV to the opposite poles of these kidneys produced minimally detectable lesions in three of them and a small lesion (1.24% of FRV) in the other (mean lesion size  $0.41 \pm 0.53\%$  of FRV). The total mean lesion size (both poles combined)

Table 1. Renal hemodynamic data for groups 1 and 2<sup>a</sup>

	Group 1 ( $n = 4$ )				Group 2 ( $n = 6$ )				Pooled Groups ( $n = 10$ )			
	Baseline		Hours after SWL		Baseline		Hours after SWL		Baseline		Hours after SWL	
	1	4	1	4	1	4	1	4	1	4		
GFR (ml/min)	10.19 $\pm$ 2.2	7.07 $\pm$ 3.3	7.77 $\pm$ 1.7	6.77 $\pm$ 1.7	8.81 $\pm$ 2.9	4.95 $\pm$ 1.2	5.17 $\pm$ 2.6	5.79 $\pm$ 2.4	9.36 $\pm$ 2.6	5.81 $\pm$ 2.4		
<i>P</i> value versus baseline (95% CI of the difference)		>0.05 (-0.59 to 6.84)	>0.05 (-0.29 to 7.14)	>0.05 (-0.29 to 7.14)		<0.05 (1.04 to 6.70)	<0.05 (0.81 to 6.47)	<0.01 (1.62 to 5.48)		<0.01 (1.64 to 5.47)		
RPF (ml/min)	50.7 $\pm$ 13.1	24.5 $\pm$ 13.0	31.3 $\pm$ 7.3	37.4 $\pm$ 15.2	37.4 $\pm$ 15.2	20.6 $\pm$ 5.8	23.6 $\pm$ 13.7	22.2 $\pm$ 8.9	42.7 $\pm$ 15.3	26.7 $\pm$ 11.8		
<i>P</i> value versus baseline (95% CI of the difference)		<0.05 (0.72 to 51.7)	>0.05 (-6.1 to 44.9)	>0.05 (-6.1 to 44.9)		<0.05 (1.53 to 32.1)	>0.05 (-1.47 to 29.0)	<0.01 (8.92 to 32.2)		<0.01 (4.38 to 27.7)		

<sup>a</sup>Data for GFR and renal plasma flow (RPF) are shown as mean  $\pm$  SD; CI, confidence interval.

in these kidneys was  $0.43 \pm 0.54\%$  of FRV, which is significantly less than the mean reported above for treatment of only one pole with 2000 SW at 24 kV with no pretreatment ( $P < 0.02$ ; 95% CI  $-8.8$  to  $-0.82$ ).

The treated kidneys of groups 1 and 2 sustained similar mean reductions of GFR and RPF at 1 and 4 h after the application of both doses of SW (Figure 4). The reductions that were observed in both variables were similar in magnitude to those that were observed after the single application of 2000 SW at 24 kV to one renal pole (5), but because the number of animals in each group was small, statistical analysis was not definitive for all time points (Table 1). Accordingly, the data from both groups were pooled for analysis (Table 1), which

confirmed the agreement between the hemodynamic responses in pretreated and nonpretreated kidneys (5).

The experiments that were conducted in group 3 tested the hypothesis that application of the low-energy SW to the same renal pole to which the higher energy SW were applied likewise protected the tissue from the usual injury. Figure 5a shows digitized and colorized cross-sectional views from three of the six kidneys that were quantified in this group. Four kidneys had lesions at our limit of resolution (0.1% of FRV); the other two lesions composed 0.34 and 0.91% of FRV. Mean lesion size for the group was  $0.28 \pm 0.33\%$  of FRV, which is significantly less ( $P < 0.01$ ; 95% CI  $-8.9$  to  $-1.9$ ) than the lesion that



**Figure 5.** Digitized images (mid-coronal plane) of three kidneys each from groups 3 (a) and 4 (b). The same pole of each kidney received the pretreatment (a, 500 SW; b, 100 SW) and the standard “dose” of SW. The circles denote F2. Hemorrhagic lesions are shown in red; cumulative lesion sizes that were measured in each pole are shown as % FRV.

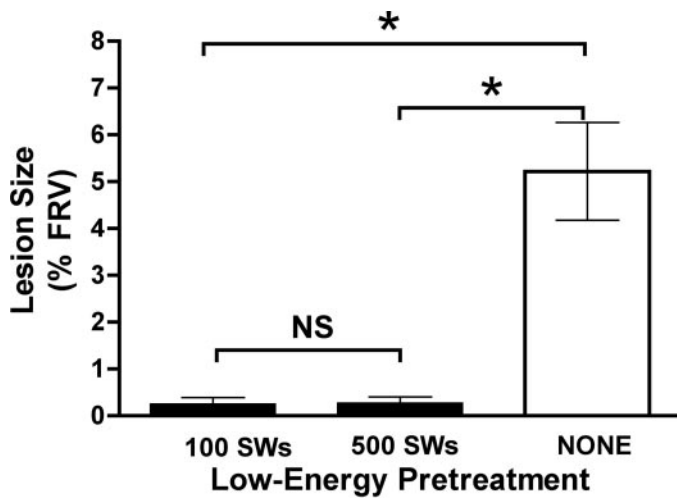


Figure 6. Mean size of lesions that were measured in groups 3 and 4 (■) and in kidneys that were treated with a single standard “dose” of SW to a single pole without pretreatment with low-energy SW (5). \* $P < 0.01$  for *post hoc* comparisons.

normally is produced by 2000 SW applied at 24 kV without any pretreatment (Figure 6).

Figure 7 shows a stained section (hematoxylin and eosin) from one of the group 3 kidneys that had a minimally detectable lesion (<0.1% FRV). A single damaged blood vessel is

evident in Figure 7a (shocked pole) amid a large expanse of tissue with no discernible indication of damage. Very few damaged vessels were seen in the cortex, whereas tubular and vascular injury was always evident in at least one papilla. Figure 7b shows a histologic section taken from the opposite, nonshocked and uninjured pole of the same kidney for comparison.

Figure 5b shows digitized and colorized views of three kidneys from group 4 in which the low-energy treatment was limited to 100 SW at 12 kV. This experiment asked whether a threshold number of SW must be administered to elicit the protective response. Lesion sizes were quantified in five of the eight kidneys in this group. Two of the lesions were at the limit of resolution (0.1% of FRV). The other three lesions composed 0.12, <0.1, and 0.94% of FRV (the mean lesion size was  $0.39 \pm 0.48\%$  of FRV). The mean lesion size for group 4 did not differ significantly from that for group 3 but was significantly less ( $P < 0.01$ ; 95% CI  $-8.2$  to  $-1.7$ ) than that for kidneys that had not received the initial low-energy treatment (Figure 6).

Figure 5 demonstrates the variability of lesion sizes that were observed between kidneys in groups 3 and 4. Figure 8, which shows three sections from one kidney in each group, presents a glimpse of the lesion as viewed within the kidneys. Each kidney shown in Figure 8 had lesions that were at or near the limit of resolution.

Figure 9 and Table 2 summarize the renal hemodynamic data

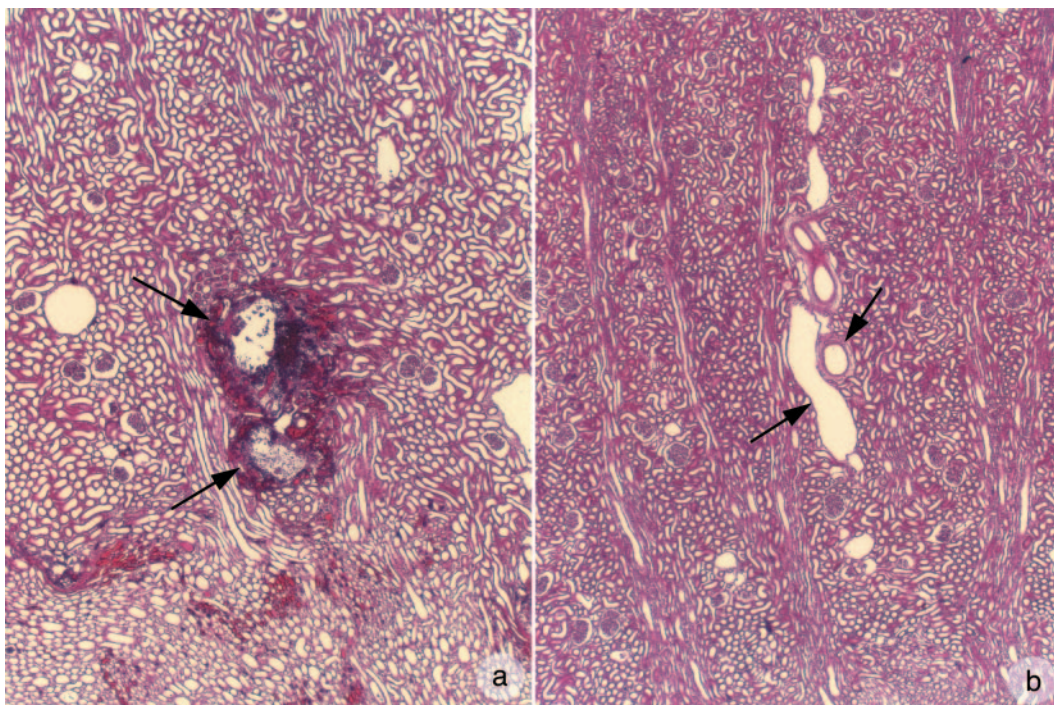
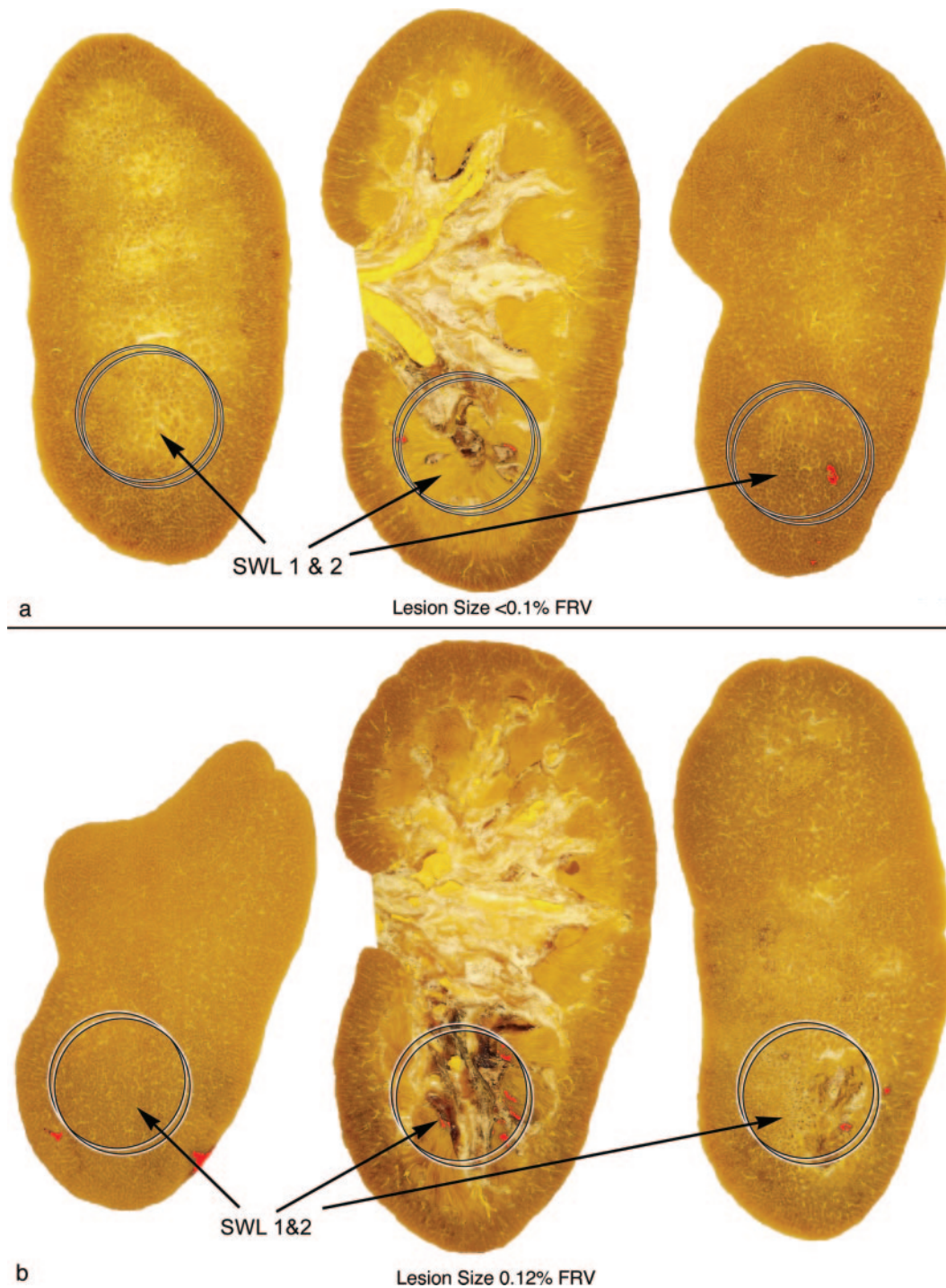


Figure 7. Light microscopic hematoxylin- and eosin-stained sections comparing tissue injury in lower and upper poles of a kidney from group 3. (a) The level of vascular damage seen in the shocked pole of a kidney that was treated with 500 SW at 12 kV followed by 2000 SW at 24 kV applied to the same location on the kidney. Note the single damaged artery and vein (arrows) in the center of the field. A ring of hemorrhage surrounds both vascular structures. The nearby nephrons and blood vessels are normal. (b) A section through the upper pole of the same kidney. No evidence of vascular or tubular injury can be seen. Note the normal profiles of several arteries and veins in the center of the panel (arrows). Magnification,  $\times 150$ .



**Figure 8.** Digitized serial-section images (coronal plane) of one kidney each from groups 3 (a) and 4 (b). The figure illustrates the distribution of lesions through the thickness of the parenchyma in each kidney (compare with Figure 1). Red indicates hemorrhage.

that were obtained from groups 3 and 4 and compares them with our previously published data (5) that were obtained from kidneys that received no low-energy treatment before receiving 2000 SW at 24 kV. Baseline GFR in groups 3 and 4 did not differ significantly from each other or from animals that had received no pretreatment (5). SWL produced similar, statistically significant reductions of GFR in both groups at the 4-h determina-

tion. However, whereas the reduction was gradual in group 3 (no significant change in GFR was seen at 1 h after SWL), the reduction was precipitous in group 4 (in which GFR was reduced by  $52.4 \pm 8.1\%$  at 1 h after SWL) and differed significantly from the corresponding 1-h value in group 3 ( $P < 0.01$ ; 95% CI  $-63.6$  to  $-8.3$ ).

Baseline values for RPF, likewise, were not significantly dif-

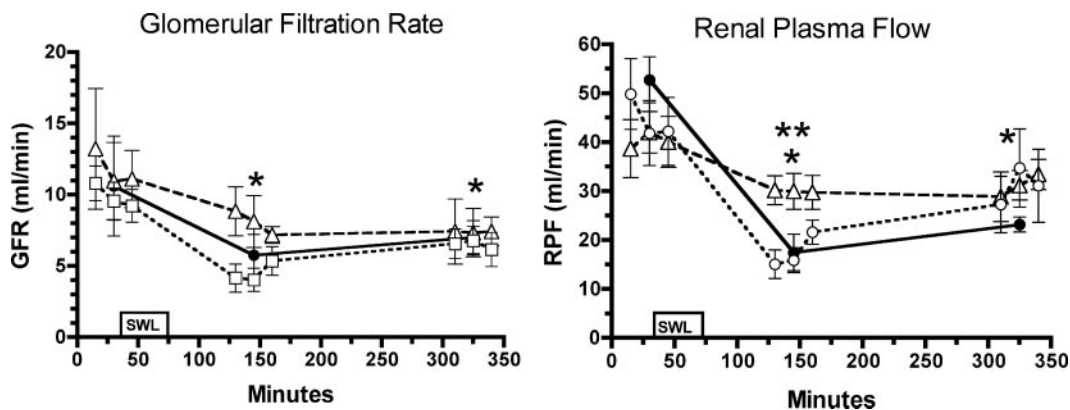


Figure 9. Renal hemodynamics measured before and at 1 and 4 h after SWL in groups 3 (dashed line) and 4 (dotted line). The data are displayed in comparison with previously published data (5) for kidneys that received only a single treatment of 2000 SW at 24 kV. See Results and Table 2 for details of statistical analysis of these data.

ferent between groups 3 and 4 and the group that received no low-energy treatment (Figure 9, Table 2). As was the case with GFR, SWL produced a relatively small reduction of RPF at 1 h after SWL in group 3 compared with the reduction that was observed at 1 h after SWL in group 4. Indeed, that reduction in group 4 was more than twice as large as and significantly different from what occurred in group 3 ( $P < 0.02$ ; 95% CI  $-58.2$  to  $-7.7$ ). RPF had returned to values that were not significantly different from baseline in all three groups at 4 h after SWL.

## Discussion

These studies confirm and at least partially characterize the protection that is provided by pretreatment of a kidney with low-energy SW against the renal injury and bleeding that ordinarily are caused by a typical dose of SW used in clinical lithotripsy. We first observed the protective response in kidneys in which opposite renal poles had been treated in succession with standard-energy SW (24 kV), which caused substantial damage to the first pole to be treated and minimal damage to the second pole (Figure 1) (10). Accordingly, the first series of experiments described in this report (group 1) asked whether the initial tissue injury or the SW, *per se*, invoked the response; *i.e.*, the first set of SW was applied at an input energy (12 kV) that caused minimal to no detectable tissue damage in the kidney (11). Because the protection occurred in this setting, too (Figure 2), we concluded that the SW, not the tissue injury that was caused by the SW, mediated the protection.

The extent of the renal injury that was caused by the SW in these studies was delineated and quantified only by morphometric analysis. Such analysis provides accurate quantitative estimates of lesion size by direct examination of the lesion (13). In retrospect, our experimental design can be criticized for failing to include an indirect assessment of renal injury, such as that provided by the assay of urinary enzymes that are released by tissue injury (16), because confirmation of the protection phenomenon in humans will necessarily require indirect methods for assessing lesion size.

Similarly, the strength of the conclusions that we have drawn

from each experiment could be criticized as merely tentative given our relatively small group sizes. The effective counterargument to this criticism, however, derives from examination of the results that were obtained in each series, in which, in comparison with lesions that were measured in nonprotected kidneys (5), differences in lesion size were large, better than marginally statistically significant, and consistent across all four experimental groups.

Such criticisms notwithstanding, the potential utility of this protective protocol in clinical lithotripsy is obvious given that the literature reports numerous instances of renal injury and impairment occurring after SWL (4). Although some practitioners may believe that the modifications made in second-generation lithotripters, *e.g.*, smaller focal zones and higher peak pressures, should reduce the incidence of renal injury and impairment—in particular, the incidence of subcapsular hematomas—the opposite seems to be the case (8,9). Indeed, Gerber *et al.* (17) recently reported lower stone-free rates and higher complication and retreatment rates for the Lithostar Plus and Modulith SLX lithotripters compared with the Dornier HM3 lithotripter. These findings are particularly relevant given that lithotripsy retreatments for incompletely comminuted stones commonly occur and undoubtedly multiply the potential for renal injury and functional impairment. Moreover, Evan *et al.* (18) recently proposed that SWL-induced renal injury, particularly to the papilla, may actually promote the growth of brushite stones, which resist breakage by lithotripsy. If this proposal holds true, then it should draw even more attention to the potential clinical usefulness of the protective phenomenon described in this report.

Given the potential clinical applicability of the protection protocol and the time required to administer the low-energy SW, during which little stone breakage would be expected, it is important to know whether fewer than 2000 low-energy SW will evoke the response. The experiments in group 2, in which 500 low-energy SW were applied as pretreatment, answered this question in the affirmative and set the stage for the experiments of groups 3 and 4, in which both sets of SW were applied to the same renal pole. The experiments of group 3



Table 2. Renal hemodynamic data for groups 3 and 4 and for unprotected kidneys<sup>a</sup>

	Group 3: 500 SW Pretreatment (n = 8)				Group 4: 100 SW Pretreatment (n = 8)				No Pretreatment (n = 9; see reference [5])			
	Baseline		Hours after SWL (Mean % Change ± SE)		Baseline		Hours after SWL (Mean % Change ± SE)		Baseline		Hours after SWL (Mean % Change ± SE)	
	1	4	1	4	1	4	1	4	1	4	1	4
GFR (ml/min)	11.8 ± 8.0	-21.8 ± 11.6	-32.1 ± 10.6	-52.4 ± 8.1	9.8 ± 2.9	-52.4 ± 8.1	-33.1 ± 7.7	10.6 ± 3.6	-39.4 ± 5.4	-9.8 ± 12.4	-39.4 ± 5.4	-9.8 ± 12.4
P value <i>versus</i> baseline (95% CI of the difference)		NS (-49.3 to 5.7)	<0.02 (-72.6 to -33.6)	<0.001 (-71.5 to -33.3)		<0.001 (-71.5 to -33.3)	<0.005 (-51.4 to -14.9)		<0.0001 (-51.9 to -27.0)	NS (-38.4 to 18.8)	<0.0001 (-51.9 to -27.0)	NS (-38.4 to 18.8)
RPF (ml/min)	40.3 ± 11.4	-21.3 ± 8.7	-20.6 ± 12.02	-54.2 ± 7.9	54.2 ± 7.9	-54.2 ± 7.9	-19.9 ± 20.7		-50.2 ± 6.0	-25.3 ± 12.1	-50.2 ± 6.0	-25.3 ± 12.1
P value <i>versus</i> baseline (95% CI of the difference)		<0.05 (-41.8 to -0.7)	NS (-49.6 to 8.3)	<0.001 (-73.0 to -36.4)		<0.001 (-73.0 to -36.4)	NS (-68.8 to 28.9)		<0.02 (-89.4 to -11.0)	NS (-53.2 to 2.6)	<0.02 (-89.4 to -11.0)	NS (-53.2 to 2.6)

<sup>a</sup>Data for baseline GFR and RPF are shown as mean ± SD and as mean % change for 1 and 4 h after SWL. SW, shock waves.

aimed at defining—and subsequently affirmed—the potential relevance of the protection protocol for human lithotripsy because ethical considerations preclude applying even low-energy SW to a portion of the kidney in which there is no stone. The SW had been applied to opposite renal poles in groups 1 and 2 to isolate and characterize the individual effects of each set of SW.

The experiments of group 4 did not identify a threshold for activation of the protective response; *i.e.*, nearly identical protective responses occurred in groups 3 and 4 after pretreatment with either 500 or 100 low-energy SW. Although it certainly would be of scientific interest to identify a threshold for the response, if one exists, the clinical point is made by these results in any case. That is, the protective response was evoked by what amounts to a minimum number of low-energy SW, and if those SW do not contribute directly to stone breakage, then they consume only a small fraction of the total treatment time while contributing substantially to minimizing the tissue injury that would otherwise be caused by the higher energy SW that are needed to break stones.

Limitations of current imaging technology make it difficult for practitioners to know when SWL has broken a kidney stone sufficiently for complete elimination of the fragments from a patient’s urinary tract. Accordingly, it is not uncommon clinical practice to administer the near-maximum or maximum allowable number of SW for a given machine to provide the highest probability of optimum stone breakage. This practice, although ensuring the best fragmentation, undoubtedly increases the risk for unnecessary renal injury and impairment because the severity of the injury that is induced by SWL is related to the number of SW administered (19,20). Accordingly, any SW that are administered in excess of the number needed to convert the stone to passable fragments increase the risk for tissue injury and complications for the patient, without therapeutic gain. On the basis of these results, the low-energy pretreatment protocol should permit the application of maximal numbers of SW to promote complete stone breakage while minimizing or at least reducing the severity of the renal injury that is caused by the SW.

The experiments described herein were not designed to identify the mechanism of the protective response. Nevertheless, the data provide some basis for speculation and future planning. The lesion that is caused by SWL is hemorrhagic (21,22); the bleeding presumably derives from blood vessels that are broken within the path of the SW (see Figure 7). Vessels of the renal papilla seem to be the most susceptible to breakage by SW (11). Accordingly, the reduced incidence of bleeding in the protected kidneys invites the hypothesis that the low-energy SW initiated some degree of renal vasoconstriction, which persisted during application of the higher energy SW. Our subsequent observation that these kidneys were vasoconstricted 1 h after SWL (Figure 9) supports (but does not prove) this hypothesis. Alternatively, the low-energy SW may have reduced the clotting time of blood issuing from vessels that were damaged by the SW. We have no data for or against the latter possibility, but the hemodynamic data in Figures 4 and 9 and earlier studies from this laboratory (5,11,23,24) and others (3,25–31) demonstrate the

occurrence of renal vasoconstriction after SWL and support the former hypothesis. Even so, because all of our measurements of renal hemodynamics were made at least 1 h after the SW had been applied, they do not answer directly the question of whether renal vasoconstriction occurred during SWL or whether vasoconstriction occurred in time to reduce the subsequent bleeding. The test of this hypothesis will require measurement of renal blood flow during the application of the low- and higher energy SW.

One interesting aspect of the hemodynamic data that were obtained from the pigs in groups 3 and 4 was that the reduction of RPF that was recorded 1 h after SWL in group 3 (500-SW pretreatment) was significantly diminished in comparison with the reductions that were noted at the same time point in group 4 (Figure 9, Table 2). Although these experiments were not designed to address the reasons behind such a difference in hemodynamic responses between groups and the difference may be merely coincidental, the observation suggests that the dynamics of the renal vasoconstrictor responses to the 100- and 500-SW pretreatments differed. One possibility is that the shocked kidneys of both groups were vasoconstricted to similar degrees by the pretreatments, *i.e.*, before measurement 1 h after SWL, and that the kidneys of group 3 (500 low-energy SW pretreatment) recovered more quickly than did the kidneys of group 4. Alternatively, it may be that the kidneys of group 3 were less severely vasoconstricted by their pretreatment regimen than were the kidneys of group 4 by theirs; *i.e.*, perhaps renal plasma flow in the kidneys of group 3 never fell to the levels reached in the shocked kidneys of group 4. If the latter hypothesis were true and if the post-SWL vasoconstriction is caused largely by the higher energy SW, then perhaps the higher dosage of low-energy SW that was given to group 3 conditioned the vasculature or the renal nerves so as to ameliorate the vasoconstriction that was initiated thereafter by the higher energy SW. Other explanations of this response clearly are possible, but full elucidation of the mechanism awaits further study.

The studies reported here were conducted with a first-generation lithotripter, in pigs, and with no kidney stones present. Although we find our data convincing, given that the protective response uniformly occurred in four independent experiments involving a total of 26 pigs, the response nonetheless should be confirmed in other laboratories, with other lithotripters, and with stones present. The inference from our studies, at least for the unmodified Dornier HM3 lithotripter, is that the protective response that was so evident here in porcine kidneys likewise will be evident in human patients with stones. Although direct morphologic analysis of human kidneys for lesions is not possible to the extent possible in porcine kidneys, sophisticated imaging studies and measurement of indirect indicators of renal injury (*e.g.*, urinary enzymes) should reveal whether the protective response also occurs in human kidneys.

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