The Effect of Discharge Voltage on Renal Injury and Impairment Caused by Lithotripsy in the Pig

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Abstract. The present study was designed to determine the effects of shock wave voltage (kV) on lesion size and renal function induced by shock wave lithotripsy (SWL) in the 6- to 8-wk-old pig. Each SWL-treated pig received 2000 shock waves at 12, 18, or 24 kV to the lower pole calyx of one kidney. A group of sham SWL pigs served as time controls. Bilateral GFR, renal plasma flow (RPF), and para-aminohippurate (PAH) extraction were measured 1 h before and 1 and 4 h after SWL in all treated and sham animals. The kidneys were removed at the end of each experiment for morphometric analysis. The SWL-induced lesion increased significantly in size as shock wave energy was increased from 12 to 24 kV. PAH extraction, a measure of tubular function, was not significantly affected at 12 kV, was transiently reduced at 18 kV, and was reduced for the duration of the experiment at 24 kV. GFR and RPF, however, were significantly and similarly reduced at the 1 h post-SWL period at all three kilovolt levels. At the 4-h post-SWL period, both GFR and RPF had returned to baseline levels. Lesion size and tubular injury were correlated with changes in kilovoltage, while changes in renal hemodynamics were already maximal at the lowest discharge voltage. These findings suggest that renal microvessels are highly sensitive to shock waves and that frank injury to tubules and vessels may be more closely related to discharge energy than is renal blood flow.

Extracorporeal shock wave lithotripsy (SWL) has been shown to be an effective and noninvasive treatment for a wide variety of upper urinary tract calculi. However, it is now known that SWL also induces significant acute kidney trauma (1) and may lead to significant long-term complications (2,3). In the clinical setting, prudent urolithiasis management should seek to minimize the trauma to the kidney while ensuring that renal calculi are effectively comminuted. To achieve this goal, it is essential to know how the parameters of delivery for shock waves influence stone fragmentation and renal injury.

It is a common clinical practice to reduce the discharge voltage (kV) of shock waves, particularly when treating children, with the hope of reducing renal injury while maintaining effective stone breakage. This practice is based on empirical judgment since few controlled studies have correlated parameters of shock wave delivery with effective stone comminution (4–10). Moreover, no study has yet determined how discharge voltage influences the effects of SWL-induced injury on renal function. Recent *in vitro* studies by Delius *et al.* (11,12) suggest that both stone fragmentation efficiency and cellular damage increase as acoustic energy (kV) delivered to F2 increases. However, it is not yet known whether these findings will correlate with actual *in vivo* effects in a clinically relevant setting.

In this study, an established animal model for shock wave injury was used to investigate how altering discharge voltage for the lithotripter influences renal function and the size of the resulting renal lesion. Such studies are important in producing objectively derived data to improve the safety of SWL for renal stone patients.

Materials and Methods

The present study was carried out with an unmodified Dornier HM-3 lithotripter (Dornier Medical Systems, Kennesaw, GA) located at Methodist Hospital, Indianapolis, Indiana. This lithotripter has an 80-nF capacitor and a focal zone (F2) of about 1.5-cm diameter × 2.5-cm length. Refurbished spark plugs (Service Trends, Inc., Kennesaw, GA) were used for all experiments and were discarded after 1000 shots. The shock waves produced by this lithotripter have been characterized in both *in vitro* and *in vivo* (in pigs) settings that mimicked clinical treatment conditions (13).

The experimental protocol used in this study was 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 Committee of the Indiana University, School of Medicine. Thirty-four animals were randomly assigned to one of four different groups: 12 kV, 18 kV, 24 kV, or sham shock wave treatment. All of the pigs (Hardin Farms) were female and were 6 to 8 wk of age at the time of treatment. Initially, the pigs were rendered unconscious with an intramuscular injection of ketamine (15 to 20 mg/kg) and xylazine (2 mg/kg). Each animal was then intubated and anesthetized with isoflurane (1 to 3%) throughout the experiment. Sterile saline was infused through an ear vein at a rate of 3% of body weight/h. The skin and muscle overlying the femoral vessels was surgically incised

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exposing each femoral artery and vein. An Intracath catheter (19-gauge; Deseret Medical, Sandy, UT) was placed in one femoral artery to monitor BP and to withdraw blood. A catheter sheath was inserted into each femoral vein to facilitate insertion of a "Cobra" visceral angiographic catheter (7 French, Cook, Inc., Bloomington, IN) into each renal vein. Placement of these catheters was aided by x-ray fluoroscopy. Samples of renal venous blood were drawn from these catheters. Electrocardiogram was also monitored throughout the experiment. Finally, the abdominal cavity was opened with an anterior midline incision to expose the bladder and posterior abdominal wall. The ureters were identified, incised, and cannulated with occlusion balloon catheters (7 French, Meditech, Boston Scientific Corp., Watertown, MA). The catheters were advanced, using fluoroscopy, to the ureteropelvic junction where the balloon was inflated and the catheter was secured in place with ties around the distal end of the ureters. These catheters were used for the controlled bilateral collection of urine (Figure 1). All skin incisions were closed with 1-0 silk suture before the start of clearance studies.

Inulin or polyfructosan and para-aminohippurate (PAH) were administered intravenously to establish and maintain plasma concentrations of 20 mg/dl inulin or polyfructosan and 1 mg/dl PAH. One hour before SWL was initiated, the first of three 15-min collections of urine was obtained from the animals. Samples of arterial and renal venous blood were obtained at the midpoint of the urine collections for clearance determinations.

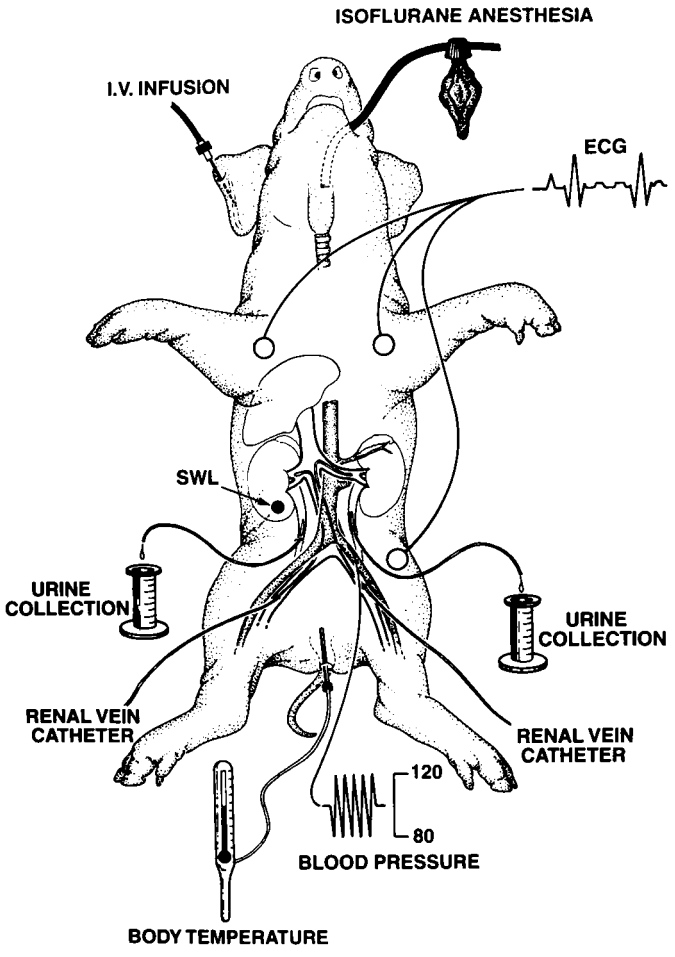

Figure 1. The physiologic setup used to determine bilateral renal function and monitor body temperature, electrocardiogram (ECG), BP, and level of anesthesia.

After the pre-lithotripsy clearances were completed, the pigs were disconnected from the anesthesia machine and transferred (unconscious) to the lithotripsy suite (a trip of about 5 min), where administration of isoflurane anesthesia was resumed and the pigs were placed in the gantry of the HM-3 lithotripter in a supine position. Sham-treated animals did not receive shock wave treatment. The animals in the 12-, 18-, and 24-kV groups were positioned in the water bath (39°C) so that the right kidney could be exposed to the shock waves. Positioning of each pig was accomplished by injecting a small amount of contrast medium (Hypaque 60%; Nycomed, Princeton, NJ) through the ureteral catheter into the urinary collection system of the kidney to be treated. Using the positioning fluoroscopes of the lithotripter, F2 was located on the lower pole calyx of the right kidney. Two thousand shocks were then delivered at 2 Hz to that kidney at the predetermined discharge voltage.

After treatment, each pig was returned to the surgical suite (once again disconnected from the anesthesia machine for approximately 5 min). Renal clearance studies were then performed 1 h and again 4 h after treatment in the same manner as outlined for the pre-lithotripsy collections. At the completion of the clearance studies, the kidneys were perfusion-fixed with 2.5% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.5, as described previously (14). After perfusion, both kidneys were removed and submerged in fresh fixative for subsequent morphologic examination (15).

Urine and plasma samples were analyzed for inulin/polyfructosan and PAH concentrations by standard colorimetric methods. Inulin/polyfructosan clearances, PAH clearance, and PAH extraction were determined and used to calculate GFR and true renal plasma flow (tRPF). These data are expressed as mean ± SEM and were analyzed by two-way ANOVA for repeated measures. The criterion for statistical significance was set at $P < 0.05$.

The complete procedure for tissue processing and determination of lesion size has been published by Blomgren *et al.* (15). The procedure will be briefly described here. The renal vasculature of the previously fixed kidney was cast with yellow Microfil, which did not contain diluent (Flow Tech, Inc., Carver, MA). The intact kidney was then dehydrated through 100% ethanol and processed overnight in chloroform. Once dehydrated, the kidney was vacuum-infiltrated with a mixture of paraffin (Paraplast X-tra; Sherwood Medical, St. Louis, MO) and barium sulfate (E-Z-Paque, E-Z-Em, Inc., Westbury, NY) at a ratio of 10:9, by weight in an infiltration oven (Shandon Hypercenter XP, Shandon, Inc., Pittsburgh, PA), followed by embedding in a paper box mold. The hardened paraffin block containing the kidney was subsequently mounted on a sliding microtome (American Optical No. 860; Leica, Libertyville, IL), and 40-μm-thick serial sections were cut in the sagittal plane of the sectioned kidney.

Statistical Analyses

Every third section of the cut kidney surface was digitally captured for image processing and analysis. The next step of this process was to use Photoshop (version 3.0, Adobe) to identify (segment) and quantify sites of intraparenchymal hemorrhage. After each image was segmented, a histogram was generated to determine the number of pixels in the lesion area *versus* that for the normal kidney tissue. These values were used to calculate total kidney area and lesion area per section. A volume fraction for the whole kidney and lesion was obtained by combining the respective areas for all slices in the database. These data are expressed as mean ± SEM and were analyzed by Welch ANOVA and Kruskal–Wallis and Wilcoxon two-sample tests. The criterion for statistical significance was set at $P < 0.05$.

Results

Table 1 shows the body weights and mean arterial BP for all four groups of pigs (shams and 12, 18, and 24 kV). Baseline mean arterial pressure did not differ significantly between any of the groups. Mean BP fell by a similar degree in all groups over the time course of the experiments.

Morphologic Observations

At the time of autopsy, the gross and histologic appearance of the SWL-treated kidneys from the three groups was strikingly different from each other and from the sham group (Figure 2). No hemorrhagic lesion was seen within the renal parenchyma at F2 or at the renal capsule of the sham-treated kidneys. In contrast, there was a detectable gross lesion on the anterior or posterior surface of the kidneys from the 12-kV group. This surface lesion was characterized by a small region of hemorrhage (<0.5 mm in diameter) or multiple sites of petechial bleeding. The lesion occurring at this site became more extensive as the voltage was increased from 18 to 24 kV. In addition, the 24-kV-treated kidney consistently sustained a subcapsular hematoma that encased the entire lower pole of the kidney, whereas only about half of the 18-kV-treated kidneys had a noticeable subcapsular hematoma. Intraparenchymal hemorrhage was evident in the kidneys of all three treated groups, but was not evident in sham-treated kidneys.

Histologic examination of the kidneys treated with 2000 shocks at 12 kV showed minimal damage at F2 compared with the large lesion induced by 2000 shocks at 24 kV (Figure 3). The injury occurring with 12 kV was localized primarily in the inner medulla and was limited to several isolated regions per papilla. There was minimal to no injury in the cortex (Figure 3, a and b). The damage in the inner medulla at 12 kV involved both microvessels and tubular segments. Disruption of the endothelial cells of the vasa recta was detected by the focal site of intraparenchymal hemorrhage noted around nearby collecting ducts (Figure 3b). Occasionally, the damaged endothelial cells were delineated by attached polymorphonuclear cells (not shown). Tubular injury ranged from mild cellular vacuolization to a complete loss of cells with disruption of their basement membrane. The vascular injury appears to have preceded the tubular injury since small regions of hemorrhage were found without any obvious tubular damage nearby (Figure 3b).

The morphologic changes induced by SWL at 24 kV included the entire region extending from the renal capsule to the tip of the papilla (Figure 3, c and d). The primary damage, disruption of the wall of veins and arteries, resulted in intraparenchymal hemorrhage that extended from the corticomedullary junction to the renal capsule. Injury to tubular cells was observed, but not as frequently as injury to the renal microvessels. Although more hemorrhage was noted in the inner medulla of the 24-kV-treated kidneys, the pattern of injury was similar to that described for the 12-kV-treated animals (Figure 3d).

The lesion volume (expressed as a percentage of functional renal volume) was quantified for each of the four groups and found to be 0.0 ± 0.0% in shams, 0.27 ± 0.27% for 12 kV, 2.28 ± 1.35% for 18 kV, and 6.1 ± 1.70% for 24 kV (Figure 4). Lesion volumes in the 12- and 24-kV groups were statistically different from each other ($P < 0.05$). The smallest lesions uniformly appeared in the 12-kV group. The largest lesions appeared in the 24-kV group (Figure 4).

Functional Observations

SWL significantly reduced GFR and tRPF in the treated kidneys (compared to baseline and to the sham group) at the 1-h post-SWL period (Figure 5) in all three SWL-treated groups regardless of kilovoltage. Both GFR and tRPF had returned to baseline values at the 4-h determination (Figure 5).

PAH extraction was measured in all four groups as an indicator of the efficiency of renal tubular secretion. PAH extraction was not significantly reduced in the treated kidneys of the sham or 12-kV groups (Figure 5), but was significantly reduced at the 1-h post-SWL period (mean change −8.49% ± 2.86%, $P < 0.025$) in the 18 kV group, and at both the 1- and 4-h post-SWL periods (−9.4 ± 2.04%, $P < 0.025$, and −6.4 ± 2.5%, $P < 0.05$, respectively) in the 24-kV group.

SWL to one kidney generally impaired renal hemodynamics in the contralateral unshocked kidneys. Small but statistically significant reductions in tRPF were evident at the 1-h post-SWL period for groups treated with 12 and 24 kV (Figure 6). Variability prevented detection of a significant difference in tRPF in the 18-kV group at the 1-h post-SWL determination (Figure 6). GFR was reduced at the 1-h post-SWL period only for the 12-kV group. These values had returned to baseline by the 4-h period. A similar downward trend in GFR during the first hour post-SWL was seen in the 18-kV group. There was no detectable impairment of PAH extraction in the contralateral kidneys or in the sham kidneys.

Table 1. Body weight and mean blood pressure (mean ± SD) of the different treatment groups

Group	Body Weight (kg)	Mean Blood Pressure (mmHg)		
		Baseline	+1 Hour	+4 Hours
Sham	13.3 ± 2.0	72.2 ± 9.6	69.9 ± 13.3	59.1 ± 11.0
12 kV	14.4 ± 4.4	66.8 ± 10.0	61.9 ± 6.8	56.4 ± 5.7
18 kV	15.4 ± 2.8	71.5 ± 9.4	65.3 ± 11.1	63.6 ± 8.1
24 kV	15.2 ± 1.6	70.7 ± 14.3	67.6 ± 10.7	52.7 ± 6.4

Discussion

The present study demonstrated that the size of the hemorrhagic lesion induced by a clinical dose of shock waves significantly increased as the discharge voltage was increased from 12 to 24 kV. Similarly, as the kilovoltage was increased, a progressively prolonged reduction of PAH extraction was observed. In contrast, tRPF and GFR were reduced to a similar degree at all three kilovoltages; that is, a progressive increase in kilovoltage did not cause any further fall in these hemodynamic parameters. These findings suggest that renal microvessels are highly sensitive to shock waves and that frank injury to

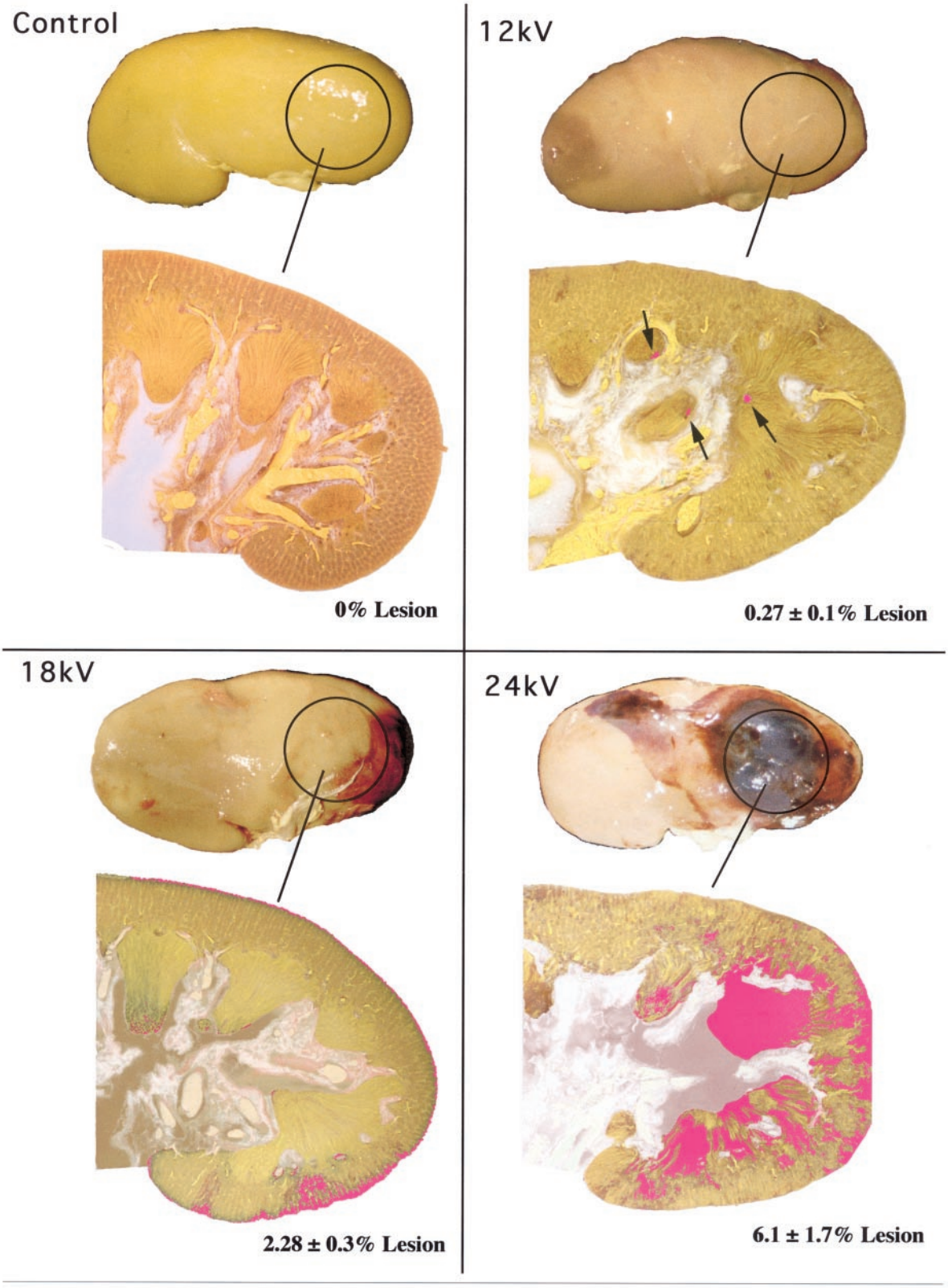

Figure 2. The gross appearance of a kidney after sham shock wave lithotripsy (SWL) or SWL at 12, 18, or 24 kV. The circles show the approximate location and size of F2 on the lower pole of each kidney. Note that no sites of hemorrhage are found on the lower pole of the sham SWL and 12-kV kidneys, but subcapsular hemorrhage is evident at 18 and 24 kV. Shown beneath the gross views of each kidney is a representative light microscopic section, mid-planar view, of the kidney and quantification of lesion size at each kilovoltage level (mean ± SEM). The lesion has been segmented and colorized (pink) so that a visual perspective for the size of the SWL-induced injury can be appreciated. Gross kidney magnification, ×0.7. Mid-planar slice magnification, ×2.

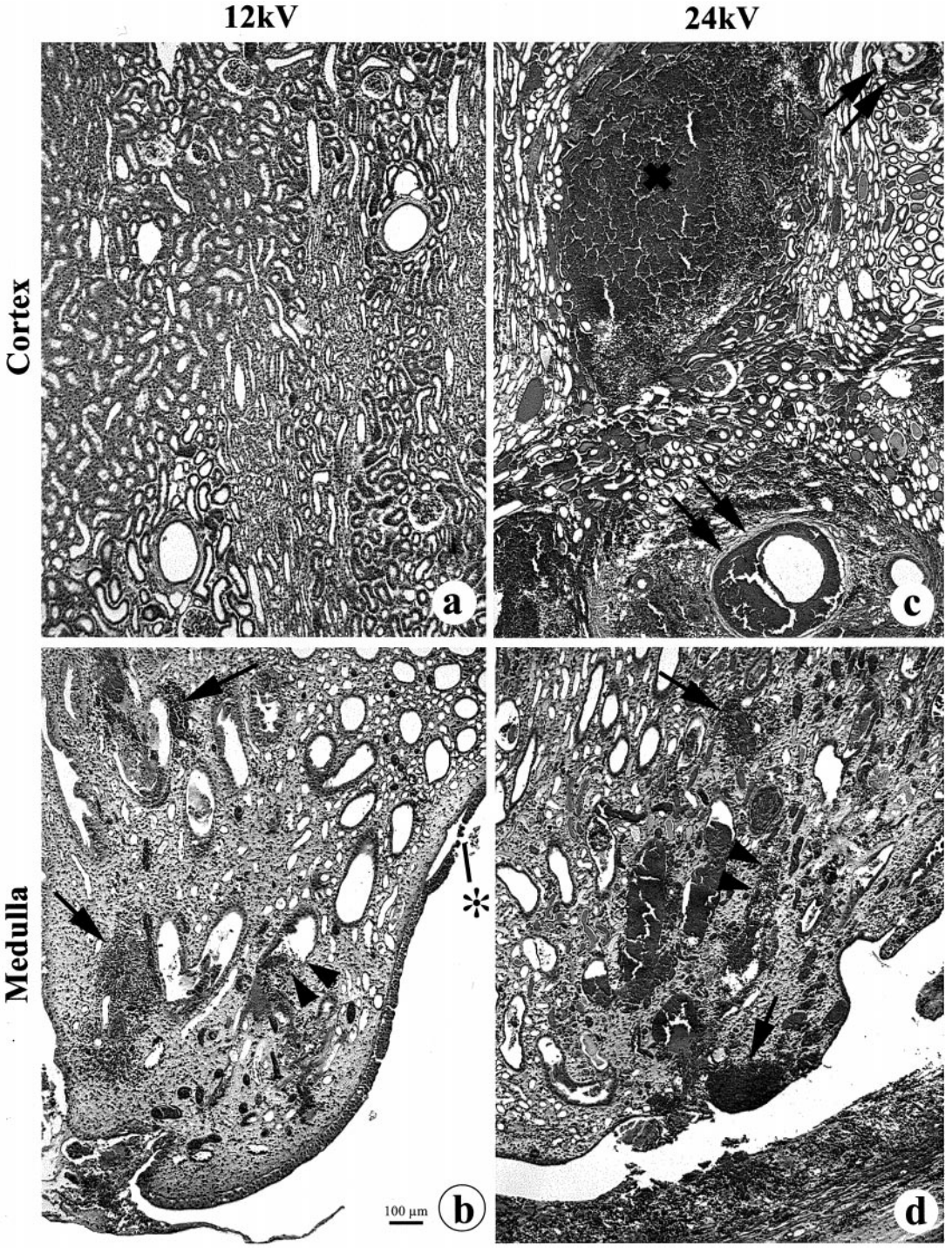

Figure 3. This series of light micrographs compare the injury seen in the cortex and medulla of an animal treated with 12 kV (Panels a and b) *versus* 24 kV (Panels c and d). The primary sites of damage induced by 12 kV were seen in focal regions in the inner medulla (Panel b) with minimal, if any changes, in the cortex (Panel a). Changes noted in the inner medulla included small sites of intraparenchymal hemorrhage (arrows) with injury of adjacent collecting ducts (arrowheads), disruption of the nearby urothelium (asterisk), and the appearance of blood in the calyceal region. At 24 kV the amount of injury seen in the medulla was greater than 12 kV; however, the major site of damage changed to the cortex where injury to veins and arteries (double arrows) resulted in massive sites of hemorrhage (X). Scale bar, 100 μm.

tubules and vessels may be more closely related to discharge energy than is renal blood flow.

The initial report from Chaussy (16) documenting kidney function in humans and dogs after SWL showed no change in function, or showed improvement in renal function following treatment. However, other groups using relatively insensitive techniques for detecting changes in renal function reported observing significant reductions in effective renal plasma flow

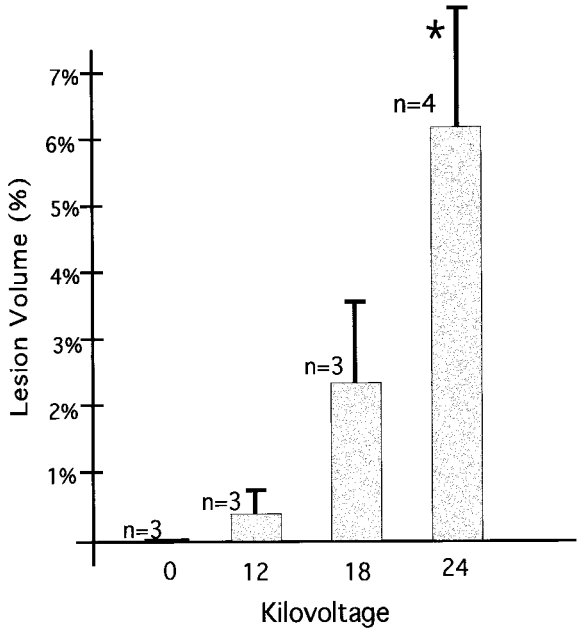

Figure 4. Effect of SWL (sham or 2000 shocks at 12, 18, or 24 kV) on lesion volume (percent functional renal volume) of the right (shocked) kidney. Data are expressed as mean ± SEM. *n* indicates the number of individual kidneys sectioned and quantified in each group. $*P < 0.05$ compared with the 12-kV group.

(RPF) and/or GFR between 24 and 48 h after SWL treatment (17–19). These reports led to a series of more well-controlled studies with more sensitive techniques in the dog (20), pig (21), and in human patients (22–26). The primary hemodynamic change these groups reported was a fall in RPF. Several of the clinical studies measured renal resistive index or followed renal blood velocity in the shocked kidney. In these studies, an increase in resistive index or a reduction in blood velocity indicative of vasoconstriction within the kidney was observed. What emerges from these studies is the view that SWL has an acute effect on renal hemodynamics through vascular injury with renal vasoconstriction.

Once it had been established that a clinical dose of shock waves consistently induced a traumatic lesion at F2, several groups examined the role of shock wave parameters (*i.e.*, shock number, kilovoltage, rate of shock wave administration, peak pressure, number of treatment sessions, and type of lithotripter) on lesion size (4–10). The parameter that appears to have the greatest influence on lesion size is kilovoltage. Close behind is peak pressure, which correlates well with kilovoltage, since kilovoltage directly influences shock wave peak pressure. Shock number was also found to influence lesion size; however, a greater increase in total shocks (doubling) was required to induce a similar increase in lesion size, which only a small increase in kilovoltage was found to achieve. Our finding that lesion size appears to be directly related to kilovoltage supports these other results.

A recent study by Roessler *et al.* has examined the effect of kilovoltage on a viable human kidney (5). These investigators determined that there was a direct relationship between kilovoltage (15 to 21 kV) and the amount of tubular and vascular injury (score of +1 to +3) detected histologically. This study did not report a change in the size of the lesion with increasing kilovoltage as we have done, but they did not employ a method to detect and quantify the lesion. We used our recently developed method that permits automated computer color segmentation of sites of hemorrhage in serial-sectioned whole pig kidneys after SWL (15). Both of these studies (5,15) suggest that the common clinical practice of lowering kilovoltage as a means of reducing the size of the SWL-induced lesion has merit.

The effect of SWL on PAH extraction changed as a function of discharge voltage. No alteration of PAH extraction was noted at 12 kV, which is consistent with the minimal amount of injury (lesion size) found in these kidneys. At 18 kV, PAH extraction was significantly reduced, but only at the 1-h post-SWL period. A reduction of similar magnitude occurred at 24 kV, but it was sustained through all 4 post-SWL hours. Thus, the greatest effect of SWL on PAH extraction occurred in the group with the highest discharge voltage. This, of course, was the group with the largest lesion. These findings are supported by an earlier study that correlated the appearance in the urine of the tubular enzyme, *N*-acetyl-β-D glucosaminidase), with the number of shock waves and kilovoltage (27). They found a highly significant correlation between the number and intensity of the shock waves and the resulting tubular damage.

Previous studies of the effect of shock wave parameters on lesion size have not determined the influence of each of these parameters on renal tubular and hemodynamic function. In a recent study, the most profound functional change noted was a 70% decrease in RPF within 1 h after 2000 shocks at 24 kV (21). GFR was also decreased at the 1-h period, but not as dramatically as RPF. Similar reductions were noted in the untreated (contralateral) kidney. These effects suggest that a vasoconstrictive event induced by shock wave treatment is altering renal function in both the treated and contralateral kidney.

The findings of the present study are consistent with our view that the primary hemodynamic change induced in the kidney after SWL at 24 kV may result from a direct insult to the vasculature interfering with the endothelial production of nitric oxide or stimulating the release of vasoactive substances such as endothelin-1 from endothelial cells, thromboxane, and other prostaglandins from platelets, or angiotensin II from renin released from renal tissue (2,21). Preliminary studies in our laboratory designed to determine the influence of shock number on lesion size and renal function corroborate the present observations (28). In general, as the shock number increases from 2000 to 4000 to 8000, lesion size increases; RPF, however, does not fall by more than the maximum noted after 2000 shocks.

Of great interest to us is the observation that even at the lowest kilovoltage studied in the present experiments, RPF was reduced to the same degree as occurred at the highest kilovoltage. This finding suggests that the renal vasculature is sensitive to the pressure wave, even at low peak pressures, and that there may also be a component of SWL-induced vasoconstriction that is not associated with frank renal injury. In support of the latter idea, the degree of damage to renal microvessels after SWL at 12 kV was minimal compared to the massive amount of injury noted to microvessels within F2 of a 24-kV-treated

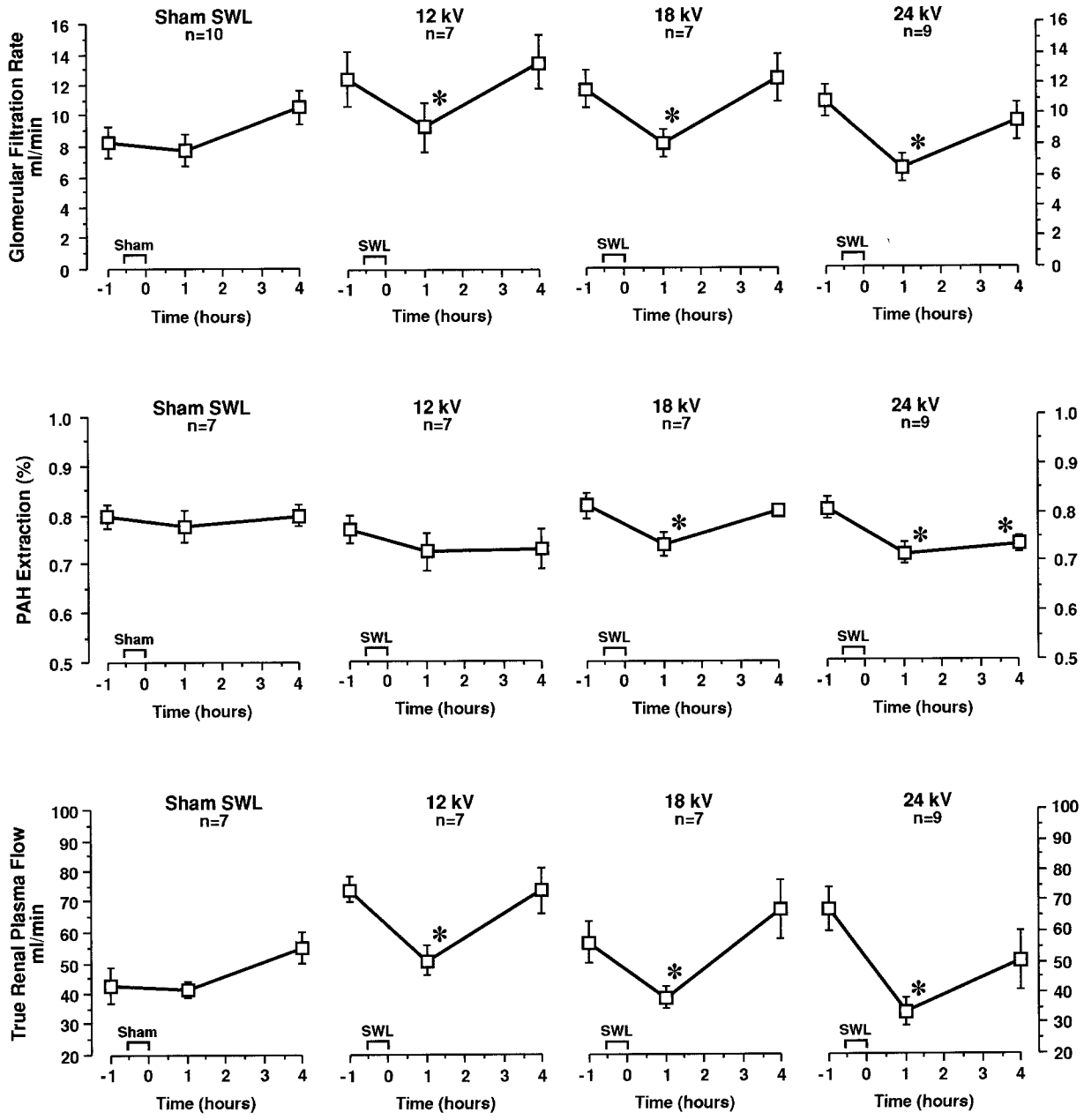

Figure 5. Effect of SWL (sham or 2000 shocks at 12, 18, or 24 kV) on GFR, para-aminohippurate (PAH) extraction and true renal plasma flow of the right (shocked) kidney. Data are expressed as mean ± SEM. *n* indicates the number of measurements (animals) for each data point. *$P <$ 0.05 compared with pre-lithotripsy period.

kidney. Thus, the vasoconstriction induced by treatment at 12 kV may have an origin separate from that induced by the hemorrhage lesion at 24 kV. The elegant *in vitro* work of Brendel *et al.* (29) supports this idea. These investigators observed vasoconstriction of all arterial segments near F2 within a few seconds after treatment with only one shock wave. The vasoconstriction lasted for 4 to 10 min and was not associated with detectable tissue injury. Although the mechanism for this response has not been studied, it may involve the sympathetic nervous system, a direct stimulation of the vascular smooth muscle cells by the pressure wave, or, perhaps, a transient release of a humoral vasoconstrictor.

Our observation that the unshocked (contralateral) kidney experiences a significant reduction in RPF (Figure 6, at 12 and 24 kV) immediately after SWL also suggests that there may be a component of SWL-induced vasoconstriction that can be separated from the hemodynamic change caused by frank renal injury to the shocked kidney. The contralateral kidneys do not exhibit detectable shock wave-induced damage to the renal parenchyma such as subcapsular hemorrhage, hematuria, or reduced PAH extraction normally associated with shocked kidneys, yet renal blood flow declines. It seems reasonable to assume, therefore, that the hemodynamic change observed in these kidneys originates from outside the unshocked kidney.

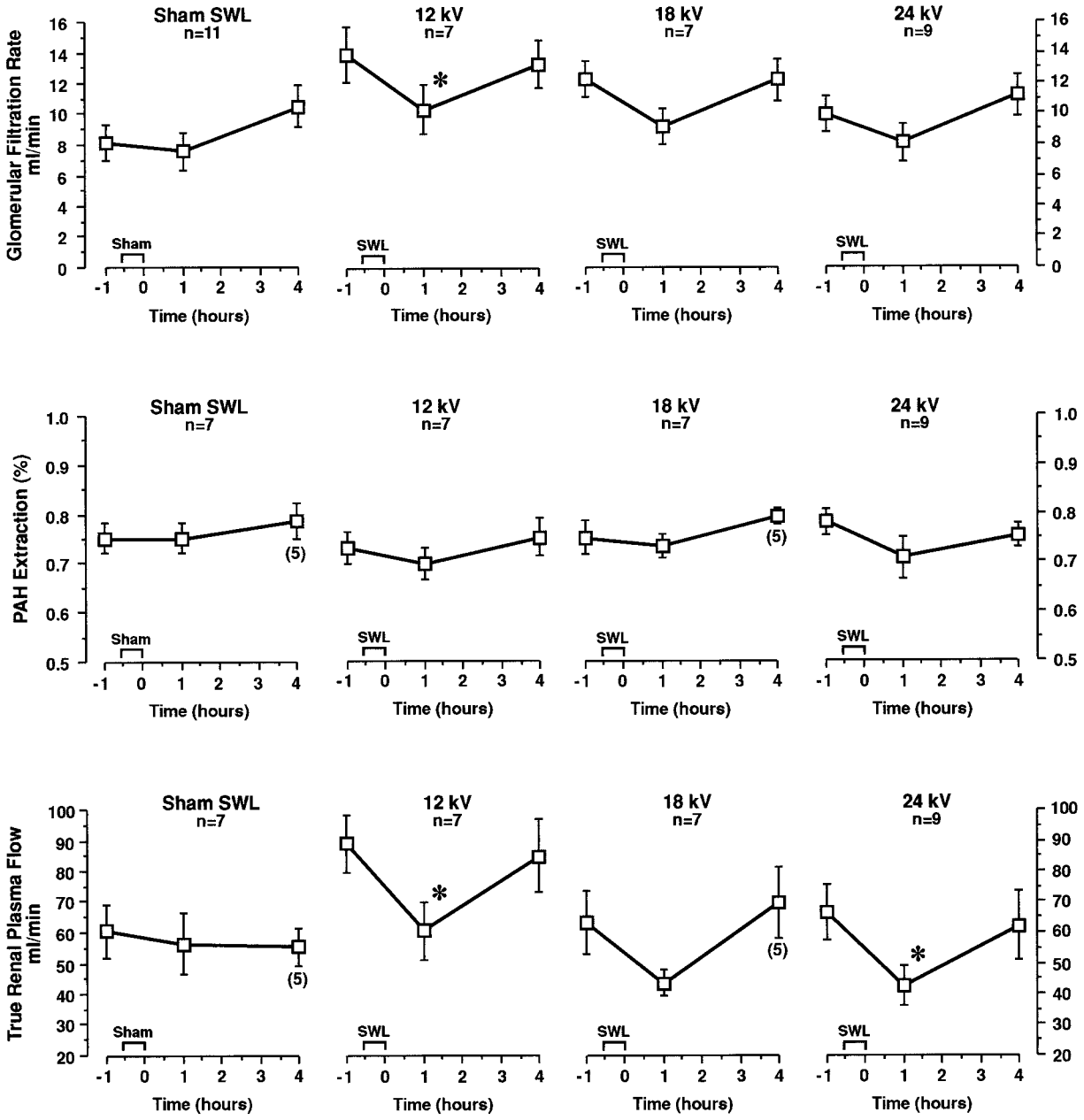

Figure 6. Effect of SWL (sham or 2000 shocks at 12, 18, or 24 kV) on GFR, PAH extraction, and true renal plasma flow of the left (unshocked) kidney. Data are expressed as mean ± SEM. *n* and the numbers in parentheses indicate the number of measurements (animals) for each data point. *$P < 0.05$ compared with pre-lithotripsy period.

There are at least two possible explanations for the reduction in blood flow. First, renal sympathetic nerves may be activated by shock waves. Second, vasoconstrictors may be released into the circulation from the treated kidney in response to the shock wave. In either case, the vasoconstrictive influence can then affect both kidneys.

Each animal in our study underwent volume expansion via saline infusion as a means to ensure adequate baseline urine output. Subsequently, the animals underwent water immersion during 20 min of SWL, which also boosts urine flow (30). With these maneuvers comes the concern that the resulting changes in renal hemodynamics and excretion may have influenced the data obtained after SWL. However, work by Epstein *et al.* (31) has shown that water immersion does not alter inulin (GFR) or PAH (RPF) clearance, and it requires a much longer time course (several hours) to cause significant natriuresis and diuresis. Additional data suggest that the renal response to mild saline-induced volume expansion is similar to that of water immersion (32).

In conclusion, the present study documents a separation between the renal vasoconstrictive response and the morphologic lesion induced by SWL. Clearly, the size of the morphologic lesion generated by SWL can be controlled by the discharge voltage. Stone comminution is achievable with the

HM-3 at both 12 kV and 24 kV. However, even the lowest discharge voltage induced a 60 to 70% reduction in RPF, which may result in an ischemic response in that kidney. Thus, there is still concern that any clinical dose of shock waves may permanently injure the kidney.

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