

## A new electromagnetic shock-wave generator “SLX-F2” with user-selectable dual focus size: ex vivo evaluation of renal injury

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**Abstract** Storz Medical AG (Kreuzlingen/Switzerland) has developed a new electromagnetic shockwave (SW) generator, the “SLX-F2”, which allows the user to choose between a small-focus, high-pressure treatment regime or a wide-focus, low-pressure option. The aim of this study was to investigate, under standardized conditions, the impact of these two different treatment regimes on SW-induced renal injury. SW-induced renal injury was investigated by using the standardized model of the perfused ex vivo kidney. SWs were applied under ultrasound control in the parenchyma of a kidney pole. Different SW numbers (20, 50, 125, 250, 500, 1,000) were applied in three groups: group A was treated with a wider focus (80 MPa), groups B (60 MPa) and C (120 MPa) with a smaller focus (each parameter setting was repeated ten-fold). Disintegration

capacity (measured by crater volume in cubes of plaster of Paris) was the same in groups A and C. After SW exposure, barium sulphate suspension was perfused through the renal artery. The maximum diameter (mm) of the extravasation in the cortex, representing the extent of vascular injury, was measured on X-ray mammography films. H&E staining was performed. In all three groups (A, B, C) a higher number of SWs caused the diameter of the extravasate to increase, with statistical significance appearing at 1,000 shots versus 20 shots ( $p < 0.05$ ). Vascular injury was not influenced by the focal size and positive peak pressure at identical SW numbers applied. Histology of the focal area showed gap-like defects. Our ex vivo data show that renal vascular injury is independent of the focal diameter of the SW generator at the same peak positive pressure and disintegration power. This confirms the in vivo findings that show renal injury caused by SW as being related to the number of SWs administered. Clinical studies are needed to investigate whether there is any advantage to offering both treatment regimes in one SW machine—for example, by using the “wide-focus, low-pressure” option for kidney stones and the “small-focus, high-pressure” regimen for stones in the ureter. The renal injury caused by either regime remains comparable.

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### Introduction

Shock-wave lithotripsy (SWL) is the treatment of choice for renal and ureteral calculi [1]. The technology is easy to use, non-invasive and effective, while patient recovery time remains short. In clinical lithotripsy, the practitioner

has control over generator voltage (kV), energy density ( $\text{mJ}/\text{mm}^2$ ), peak pressure (MPa), rate of SW administration, number of SWs and the type of lithotripter. Although numerous basic research studies have been performed, the parameters determining the extent of renal injury have yet to be fully clarified. Technical improvements in SW technology have mainly been made with an eye to providing user convenience and multifunctionality, rather than a mechanistic understanding of stone comminution and tissue injury. In fact, the long-term clinical consequences of SWL with respect to renal injury are still under investigation.

A new electromagnetic generator called “SLX-F2” has been developed by Storz Medical AG (Kreuzlingen/Switzerland). It allows the user to select either a small-focus, high-pressure treatment regime or one that uses a wide focus and low pressure. The aim of this study was to investigate, under standardized conditions, the impact of these two different treatment regimes on SW-induced renal injury.

## Materials and methods

### Shock-wave generator

The tests were performed using an experimental prototype of the SLX-F2. Shock waves (SWs) were induced by an electromagnetic cylinder and focused with a parabolic reflector (diameter 300 mm, focal distance 165 mm).

The focal size depends on the aperture and parabolic shape (both fixed) of the focussing reflector and the wavelength  $\lambda$  of the emitted acoustic pulse. A longer wavelength corresponds to a larger focus width  $F_x$ :

$$F_x = c\lambda xz/A$$

with  $c$  being a constant,  $z$  the focal distance and  $A$  the aperture. A detailed description and discussion of the physics behind this correlation can be found in [2–4].

The discharge of a high-voltage capacitive pulse forming network (PFN) results in an electrical pulse in the kilo amperes range passing through a cylindrical coil that is surrounded by a metallic membrane. This induces strong eddy currents and causes the membrane to elongate, emitting a cylindrical wave. A metallic reflector that is fixed in shape, i.e. fixed focal distance  $z$  and aperture  $A$ , focuses the cylindrical wave. The wavelength  $\lambda$  depends on the electrical characteristics of the pulse-forming network.

Two pulse-forming networks were used in the new shock-wave generator SLX-F2. The first PFN, *SLX-F2 small focus* (treatment groups B and C), is identical to that

of the series production models, SL 10 and SLX. The second (additional), PFN, *SLX-F2 large focus* can be activated by a switch to obtain a wider focus and lower peak pressure (treatment group A).

### Experimental protocol

Level 5 (group B) and level 7 (group C) are two of the energy levels for the SLX (=SLX F2 *small focus*) that are widely used in the treatment of kidney stones and were thus selected for the experiment. We measured the peak positive pressure distributions (PPP in MPa), energy flux density ( $\text{mJ}/\text{mm}^2$ ), in vitro disintegration capacity and renal injury (see below). In order to investigate and compare the influence of the focal size on disintegration capacity and renal injury, we also selected a large-focus, low-pressure regime (group A) with an identical energy flux density to group C (small-focus) and a comparable, but slightly greater disintegration capacity (Table 1; derived from unpublished data). Throughout the in vitro and ex vivo experiments, SWs were released at a frequency of 1/s.

### Pressure measurement

Positive peak pressure (PPP in MPa) and energy flux density ( $\text{mJ}/\text{mm}^2$ ) in the focal area were measured using a fibre (diameter 0.1 mm) optic laser hydrophone in degassed water (temperature  $22 \pm 2^\circ\text{C}$ ; gas content  $<1 \text{ mg/l}$ ). The fibre was mounted on an  $x$ - $y$ - $z$  table and positioned in 0.02 mm steps.

### Disintegration capacity in vitro measurement

Disintegration capacity was analysed by measuring the volume of the crater in cubes of plaster of Paris (size  $35 \times 35 \times 17 \text{ mm}$ ; Heraeus Kulzer Moldano-Blue-Stone Type 3; 207 g) after predetermined a number of SW shots. The cubes were placed in the focal zone of the therapy head in an open water bath containing degassed water (temperature  $22 \pm 2^\circ\text{C}$ ; gas content  $<1 \text{ mg/l}$ ). SWs travelled horizontally through the cubes. In order to have reasonably sized craters, but not destroy the cubes completely, 200 shots were used in group B and 50 shots were used in groups A and C (disintegration capacity is considerably higher in group A and C—the cubes would have been destroyed completely by 200 shots—as compared to group B). The crater in each cube was measured 5 times by filling it with fine-grained sand and weighing this sand on a scale that is exact to  $\pm 0.0001 \text{ g}$ . (Mettler model AE260). Results are given as the mean value  $\pm$  standard deviation of the weight of sand per shot (Table 1).

**Table 1** Positive peak pressure, focal size, energy flux density and disintegration capacity of the three groups

	PPP (Mpa)	Focal size <sup>a</sup> (mm)	Energy flux density (mJ/mm <sup>2</sup> )	Disintegration capacity (mg/shot)
Group A	80	4.5	2.3	5.4 ± 0.5
Group B	50	4.5	1.2	1.3 ± 0.2
Group C	120	2.7	2.3	4.3 ± 0.5

<sup>a</sup> -6 dB

### Renal injury-ex vivo experiments

Kidneys were obtained from freshly slaughtered pigs within 10 min. The perirenal fat was removed; the renal capsule was kept intact on the renal surface. Renal artery, vein and ureter were cannulated, then perfused with cold (4°C) 0.9% saline solution (+5,000 I.E. heparin) under physiological pressure conditions (~80 mmHg), in order to flush the kidney free of blood and achieve a fast cooling of the renal parenchyma. These prepared kidneys were stored in cold (4°C) physiological saline solution for a maximum of 4 h.

To complete the experimental setup, the kidneys were heated to 37°C in the perfusion solution before the trial started. During the trials, they were continuously perfused at 100 ml/min with isotonic sodium chloride solution through the renal arteries at a pressure of between 80 and 120 cm H<sub>2</sub>O using a commercial medical perfusion pump (Fig. 1).

In order to couple up the shock waves, the kidneys were immersed into degassed water (37°C). Shock waves were applied vertically under ultrasonographic control (B-mode, 3.5 MHz transducer) in the center of the cortex of each

kidney pole. Different treatment parameters were used for the upper and lower pole of each kidney (20, 50, 125, 250, 500 and 1,000 SW in each group A, B and C). Each parameter setting was repeated ten times and each kidney pole was treated only once. The operator had no knowledge of the respective generator settings. Ten kidneys served as controls, i.e. perfusion only, no SW application, in order to exclude artificial vessel lesions caused by the perfusion of the isolated kidney.

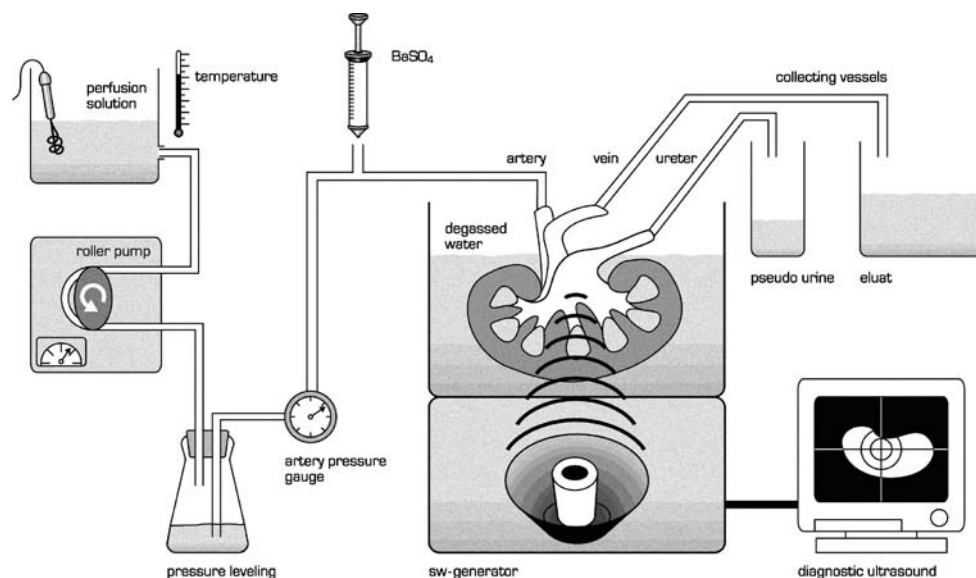
After SW exposure, barium sulphate (BaSO<sub>4</sub>) suspension was perfused through the renal artery until it exited out through the renal vein, indicating complete perfusion. The kidneys were cut into plane parallel slices, 5 mm thick, using a rotary knife. Vessels and extravasation were documented by X-ray on mammographic film. The X-ray images were investigated by a person experienced in this type of analysis, but not otherwise involved in the experiment. The maximum diameter (mm) of the extravasation in the cortex, representing the extent of vascular lesion, was measured.

### Histology

Tissue samples in the focal area were excised and fixed in 10% formalin, sectioned and embedded in paraffin, cut to 5 µm and stained with hematoxylin & eosin (H&E). Untreated tissue (control group) was prepared in the same way. The pathologist (R.G.) was not told which generator setting was used.

### Statistical analysis

The data are given as mean ± SD. Statistical analysis was performed using the SAS statistical software package,

**Fig. 1** Experimental setup

release 8.2 (SAS Institute, Cary, NC). Pair-wise  $t$  test and ANOVA were the procedures used. A value of  $P < 0.05$  was considered to be statistically significant.

## Results

### Pressure measurement

Pressure distributions and energy flux density are given in Table 1. With the additional HV switch in the off position, the acoustic output characteristics remain unchanged, so the SLX/SL 10 and the *SLX F2* small-focus regimes are identical in this respect. With the HV switch in the on position, the electrical pulse is stretched, and the acoustic pressure pulse is longer. Consequently, the focal width and the focal length increase.

### Disintegration capacity (Table 1)

Using the *SLX-F2* small-focus size, disintegration capacity increased along with higher energy levels (groups B and C). Disintegration capacity was nearly the same in groups A and C. This means that the same disintegration capacity can be achieved with lower peak positive pressure and a larger focus as with higher peak pressure and a smaller focus. Figure 2 shows the disintegration patterns of all three groups. The crater induced by the small-focus was smaller and deeper than that induced by the wide focus.

### Ex vivo renal vascular injury

Untreated kidneys ( $n = 10$ ) showed complete arterial and venous circulation without any sign on the X-ray films of vessel constriction or extravasate of barium sulphate due to vessel injury (Fig. 3a). In the treated kidneys, extravasate

of barium sulphate was seen on all X-ray films (Fig. 3b). In all three groups (A, B, C), a higher number of SWs caused the diameter of the extravasate to increase, with statistical significance appearing at 1,000 shots versus 20 shots ( $P < 0.05$ ). Vascular injury was not influenced by the focal size and the PPP, as statistical analysis showed no differences between the groups (Fig. 4) when an identical number of SWs was applied. Given identical disintegration capacities, there was no increase in renal injury in either group A (using a larger focus size and lower pressure) or group C (smaller focus and higher pressure).

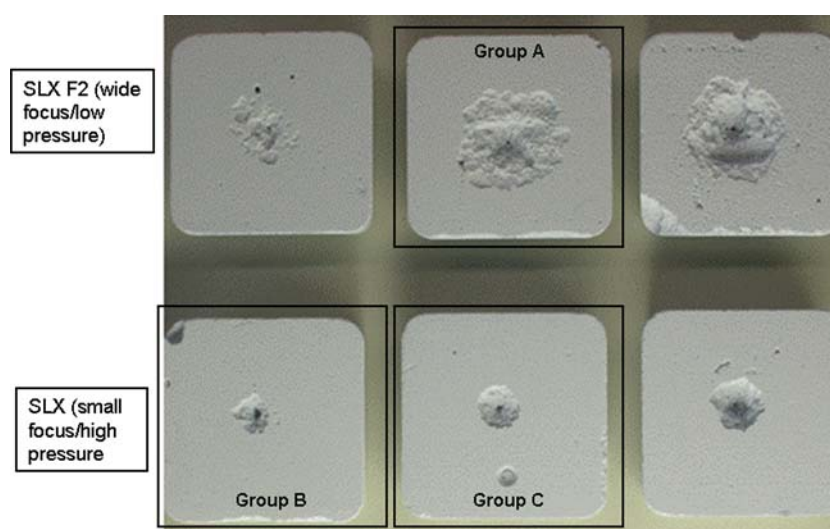
### Histological findings

In the control group, no circumscribed or focal changes in the anatomical morphology were seen. Barium sulphate was seen inside the arteries, arterioles, bowman capsule, tubules, collecting duct and veins, indicating complete circulation. The absence of disrupted vessels indicated complete circulation at physiological pressures (Fig. 5a). The tubular structure in the proximal epithelium was well-preserved, even though it is very sensitive to hypoxia. Histological analysis of the focal area after SW application showed gap-like defects and extravasation of barium sulphate (Fig. 5b). The histological defects primarily affected the tubular system and peritubular capillaries, although, in some cases, damage to the glomerular capillaries could also be observed. A loss of contrast medium was identified in perilesional tubular lumina but not in the interstitial stroma.

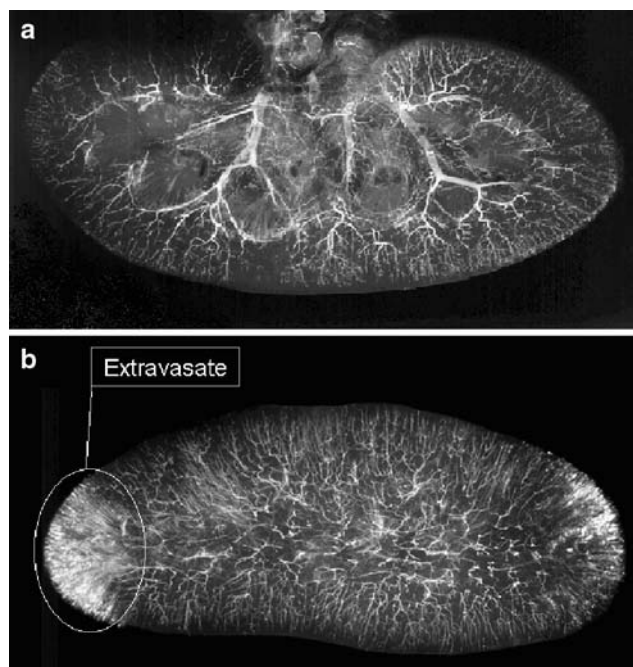
## Discussion

Expertise on the biological effects of SWL on renal tissue is mostly derived from animal studies. Currently, the pig is felt to be the most appropriate for SWL bioeffect in vivo

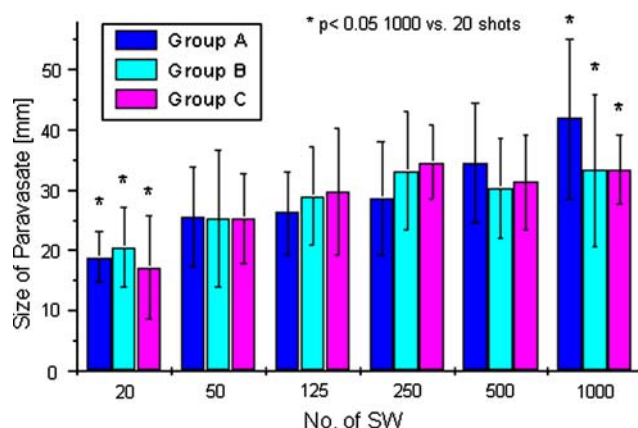
**Fig. 2** Disintegration patterns measured with cubes of plaster of Paris at different energy levels and focal sizes (*bottom row* SLX F2 small focus, *top row* SLX-F2 large focus). Energy levels used for the quantification of the renal injury are framed





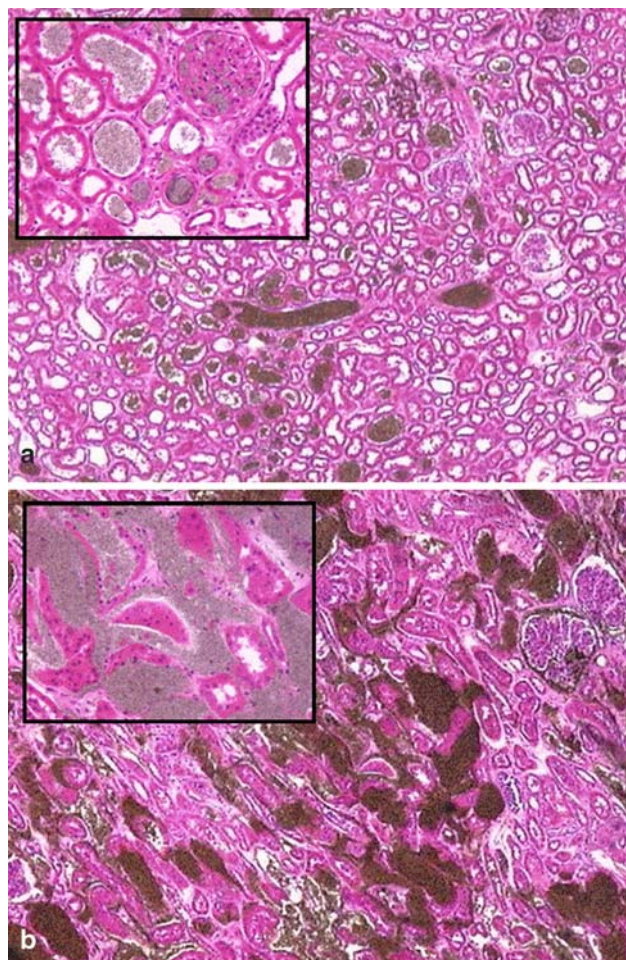


**Fig. 3** **a** Angiography of control group. **b** Angiography of treatment group



**Fig. 4** Extent of vascular injury

studies, as porcine kidneys mimic human kidneys both in size and morphology [5]. However, animal trials for testing SWL-induced renal injury have several disadvantages. The interindividual variance in the animals is largely due to non-predictable artifacts such as shock wave attenuation (absorption, reflection) from the intracorporeal path and respiratory movement of the kidney. Furthermore, the number of experiments is limited because of high costs and administrative barriers (ethics committee). To overcome these limitations, ex vivo kidney tissue models were developed by Köhrmann et al. [6] and Bergsdorf et al. [7] for the purpose of evaluating SWL-induced renal injury. These models have proven easy to handle, are low-costs



**Fig. 5** **a** Histology of control group. **b** Histology of defect renal tissue in the focal area

and have the potential of providing large series of experiments under standardized conditions and therefore reduce animal trials. However, the ex vivo findings are not directly transferable to the conditions of clinical lithotripsy and the experimental setting does not reflect the clinical usage of SWL, as the kidneys are isolated and denervated (no influence on the vegetative innervations of the vessels), respiratory movements are excluded, and interfering tissue (muscle, fat) is extracted. This disadvantage may also be regarded as an advantage, as the model excludes these unpredictable influences. We used the ex vivo model as described and evaluated by Köhrmann et al. [6].

Our ex vivo study confirms the histological results of in vivo studies that revealed vascular and parenchymal injury at and near the focus, with veins and arteries showing varying degrees of damage [5, 8–10]. The tubular injury induced by SWL involves disruption of the tubular epithelium and the associated basement membrane.

Our ex vivo study also confirms in vivo findings showing that the numbers of SWs intensifies renal injury.

Delius and colleagues [9] first reported this correlation. Several other groups [11–13] have confirmed these findings, while others observed no quantitative differences in renal injury when different amounts of SWs were applied [6, 14–16]. However, the direct comparison of these results may include systematic errors, as a large variety of lithotripters was used the different animal models (rat, rabbit, dog, pig). A recent in vivo study performed by Willis et al. [5] confirms that the number of shock waves influences renal injury. Most recently, Connors et al. [17] could show in vivo that a lower number of shock waves decreases lesion size and functional changes dramatically. They concluded that SW number should be reduced to the lowest number that fractures kidney stones in order to minimize renal injury and functional impairment.

Delius and associates [18] have reported the influence of the SW rate on renal injury. Generator voltage (kV) may be another important factor [8, 15, 19, 20]. These groups discovered that the renal injury increased along with generator voltage. Generator voltage mainly determines the peak pressure in the focal zone, although all other physical parameters of the SW (i.e. negative pressure, shock wave energy, intensity) are also affected. Thus, it is unclear which physical parameter is responsible for the vascular injury. Interestingly, Bergsdorf et al. [7] were able to show in a similar ex vivo model compared to the one used by us, that the energy density of the applied SW had a direct influence on the grade of renal vascular lesion. Their findings also correlate to the grading of renal tissue lesion in a canine model [15].

To our knowledge, there are no reports available on systems used to investigate the influence of focal diameter and positive peak pressure on SWL-induced renal injury. Our preliminary ex vivo results show that the extent of renal injury is not influenced by positive peak pressure and focal size. Traditionally, the focus size is given by the manufacturer as the full width at half the maximum force (–6 dB) of the lateral and axial pressure distribution i.e. the peak pressure in the focus. For example, Teichman et al. [21] quote the –6 dB focus size of the HM3 as 15 × 90 mm at a peak pressure of 31.1 MPa and the focus size of the SLX as 6 × 28 mm at a peak pressure of 105.6 MPa. Accordingly, the pressure at half the maximum force is 15.5 MPa for the HM3 at a focal width of 15 mm, but 52.8 MPa for the SLX at 6 mm, which is much higher than anywhere in the HM3 pressure field. In comparison, the focal width of the SLX at 15.5 MPa is also 15 mm. This means that the –6 dB focus width is not a useful figure for comparing lithotripters.

The exact mechanism that triggers SW-induced renal injury is as yet unknown. Two different mechanisms have been proposed: shear stress due to shock front distortion [22] and the cavitation that is induced inside blood vessels,

in particular, by the expansion of intraluminal bubbles [23, 24]. SWs produce cavitation bubbles that collapse with great force. These bubbles have been shown to pit metal foils and lyse isolated cells [25]. In vitro studies also indicate that the expansion of cavitation bubbles can cause model vessels to rupture [23, 24]. In this context, Evan et al. [26] have shown, that SW renal injury is reduced when cavitation/intraluminal bubble expansion is suppressed. These findings support the idea that cavitation plays a prominent role in SW-induced renal injury. Williams et al. [27] suggested that each cavitation bubble could increase its volume and destruction-potential. This is induced by the following shock waves hitting the already existing bubble (cavitation nucleus). This may explain in part the correlation of renal injury and number of SWs administered.

## Conclusions

The technical features of the new *SLX-F2* SW lithotripter allow the user to switch from a “wide-focus, low-pressure” treatment regime to one that uses high pressure and a small-focus. The renal injury caused by either regime remains comparable. Our ex vivo data show that renal vascular injury is independent of the focal diameter of the SW generator at the same peak positive pressure and disintegration power. This confirms the in vivo findings that show renal injury caused by SW as being related to the number of SWs administered. Clinical studies are needed to investigate whether there is an actual advantage to offering both treatment regimens in one SW machine—for example, by using the “wide-focus, low-pressure” option for stones in the kidney, and the small-focus, high-pressure regimen for stones in the ureter.

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