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Dual-head lithotripsy in synchronous mode: acute effect on renal function and morphology in the pig

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OBJECTIVE

To assess the effect of dual-head lithotripsy on renal function and morphology in a pig model of shockwave (SW) injury, as lithotripters with two shock heads are now available for treating patients, but little information is available with which to judge the safety of treatment with dual pulses.

MATERIALS AND METHODS

A dual-head electrohydraulic lithotripter (Duet, Direx Corp., Natick, MA, USA) was used to treat the lower renal pole of anaesthetized pigs with a clinical dose of SWs (2400 dual SWs; 10 kidneys) delivered in synchronous mode, i.e. both heads fired simultaneously. For comparison, pigs were treated with either 2400 SWs (12 kidneys) or 4800 SWs (eight) with a conventional electrohydraulic lithotripter (HM3, Dornier, Wessling, Germany).

RESULTS

Dual-pulse SW treatment with the Duet lithotripter caused a decline in the mean (SD) glomerular filtration rate (GFR) of 4.1 (1.9) mL/min, with a trend for the effective renal plasma flow (RPF), at 31 (19) mL/min, to also decrease. These changes in renal haemodynamics were similar to the decreases in GFR and RPF in response to treatment with the HM3 lithotripter with 2400 SWs, at 4.8 (0.8) and 32 (10) mL/min, respectively, or 4800 SWs, at 5.4 (1.0) and 68 (14) mL/min, respectively. Linear association analysis showed that the functional response to dual-pulse SWs was more variable than with conventional SWs. Morphological quantification of kidney damage (expressed as a percentage of functional renal volume, FRV) showed that tissue injury with 2400 paired SWs with the Duet, at 0.96 (0.39)% FRV, was similar to injury produced by either 2400 single SWs, at 1.08 (0.38)% FRV, or 4800 single SWs, at 2.71 (1.02)% FRV, with the HM3. However, morphological damage was less consistent with the Duet (measurable in only five of eight kidneys) than that with the HM3 (measurable in all 12 kidneys). Acoustic output and the timing of dual SWs in synchronous mode increased in variability as the electrodes aged, affecting the amplitude and targeting of focal pressures.

CONCLUSION

With the caveat that variability in the timing of dual SWs will unpredictably alter the distribution of SW energy within the kidney, this study shows that a clinical dose of dual-head SWs delivered in synchronous mode elicits a renal response similar to, but more variable than, that with a clinical dose of SWs from a conventional electrohydraulic lithotripter.

KEYWORDS

lithotripsy, kidney, haemodynamics, morphology, acoustic waves

INTRODUCTION

Lithotripters with two treatment heads have recently been approved by the US Food and Drug Administration (FDA). One such machine, the Duet (Direx Corp. Natick, MA, USA), can be operated so that the two heads are fired in sequence (alternating mode), or simultaneously (synchronous mode) at up to 120 shock waves (SWs)/min per head. Thus, this lithotripter can deliver 240 SWs/min, twice the number typically administered with a conventional lithotripter [1]. The manufacturer indicates that this is a significant advantage, to reduce overall treatment time while working within accepted limits for SW rate (http://www.direxusa.com).

Lithotripsy using dual-treatment heads was introduced to investigate the role of cavitation in SW action [2]. Studies with a system in which identical electrohydraulic shock sources were aligned directly facing one another showed that the timing of paired pulses could be used either to suppress bubble expansion, if the time delay was minimal, or enhance the force of bubble collapse, if the delay was somewhat longer [2]. This led to techniques in which tandem SWs were delivered along the same axis, with the trailing pulse precisely timed to interact with the cavitation initiated by the first pulse [3–5]. This work suggested that, with proper timing, the trailing SW can be used to suppress the cavitation associated with vascular trauma [6]. For those interested in reducing treatment times in lithotripsy, using tandem pulses delivered along the same axis has the limitation that the firing rate of an individual shock source is limited to 120 SWs/min by the FDA. Thus, dual-head lithotripsy in which both sources can be fired at 120 SWs/min is seen as a potential way of achieving improved stone breakage and reducing overall treatment times [7].

Safety is a key issue in SW lithotripsy (SWL), and many reports have shown that SWs produce vascular trauma to the kidney [8,9]. Acute damage can progress to a permanent loss of functional renal tissue, and SWL trauma has been linked to significant long-term effects [8–10]. The severity of trauma depends on pulse energy [11] and SW number

[12], and there is evidence suggesting increased injury with lithotripters that use a narrow focal zone [13,14]. Thus, the trauma depends on the acoustic characteristics of the lithotripter.

A lithotripter that uses two heads creates conditions different from those produced by a conventional lithotripter; an individual treatment head of a dual-head device might be similar to that of a conventional machine, but SWs pass along two paths through the body, not one, and if the two heads are triggered so that the SWs interact, the acoustic field will be different [2,15]. However, virtually all that is known of trauma in SWL comes from experience with conventional lithotripters.

Accordingly, in the present study we characterized the renal response to SWs delivered with a dual-head electrohydraulic lithotripter. A typical clinical dose of SWs was given in synchronous mode to an established porcine model of renal trauma and function [11]. The renal response was compared to treatment with the same number of SWs delivered with a conventional electrohydraulic lithotripter.

MATERIALS AND METHODS

Adult female pigs (45 kg; Hardin Farms, Danville, IN, USA) were anaesthetized (15–20 mg/kg ketamine and 2 mg/kg xylazine for induction and intubation followed by 1–3% isofluorane and 100% oxygen for maintenance) and prepared for renal functional measurements as described previously [16]. Catheters were placed into an ear vein for the i.v. infusion of fluids, the infrarenal aorta for monitoring blood pressure and sampling arterial blood, both renal veins for sampling renal venous blood and both ureters for collecting urine. Isotonic saline was infused i.v. (1% of body weight/h) throughout the experiment to maintain adequate hydration and urine flow. Inulin and para-aminohippuric acid (PAH) were infused i.v. at 70 mL/h.

For studies with the Duet lithotripter, the pig was placed supine on the motorized, adjustable treatment table of the Duet system. The water cushions of the two treatment heads were coupled to the flank of the pig using castor oil as the coupling medium. Baseline cardiovascular and renal function measurements were begun 30 min later, and consisted of two 25-min clearances. Radio-contrast medium was injected through the left ureteric catheter and the focal zone of the lithotripter was targeted by fluoroscopy on the lower-pole calyx of the left kidney. The study compared control pigs (not treated with SWs) and pigs given 2400 SWs from each treatment head in synchronous (simultaneous) mode (17 kV, 120 SWs/min) using one pair of electrodes. Direx recommended this regimen as representative of clinical treatment in synchronous mode. Lithotripsy was temporarily stopped every 500 SWs to confirm targeting. Two 25-min clearances were obtained following a 1-h recovery period after lithotripsy.

For studies with the HM3 lithotripter (Dornier, Wessling, Germany) baseline cardiovascular and renal function measurements were begun 30 min after completing all surgery and consisted of two 25-min clearances. The pig was disconnected from the anaesthesia machine and transferred (unconscious) to the lithotripsy suite (taking ≈ 5 min) where administration of isofluorane was resumed and the pig placed supine in the patient gantry of an unmodified HM3 lithotripter. The second focal point (F2) was targeted on the lower-pole calyx of the left kidney using fluoroscopy and aided by administering radio-contrast material into the collecting system via the left ureteric catheter. The study compared pigs not treated with SWs with pigs given either 2400 or 4800 SWs at 24 kV, 120 SWs/min. The latter group was included because both heads of the Duet delivered a combined total of 4800 SWs to the kidney. The position of F2 was checked every 500 SWs with the lithotripter in standby mode, and the electrode changed at every 1000 SWs. The pigs were returned to the surgical suite for two 25-min clearance measurements beginning 1-h after lithotripsy.

To measure renal function, plasma and urine samples were analysed for inulin and PAH, and their renal clearances used to estimate the glomerular filtration rate (GFR) and effective renal plasma flow (RPF), respectively. The renal extraction of PAH (arterial-renal venous PAH difference, EPAH) was measured and provides an estimate of the efficiency of renal tubular PAH transport.

For morphological analysis, the kidneys were perfusion-fixed *in situ* at the end of the experiment [17], and processed for histology and morphological analysis, as previously described [18]. Lesion sizes were measured for eight of 10 kidneys in pigs treated with the Duet (2400 SWs), six of 12 pigs given 2400 SWs with the HM3, and six of eight pigs given 4800 SWs with the HM3. The lesion size was expressed as a percentage of functional renal volume (FRV) determined by computer-assisted segmentation of digital images from serial sections (120 μm) of the entire kidney. The kidneys used to quantify lesion size could not be used for routine histology because different tissue preparation methods are required. Kidneys for histological analysis were embedded in paraffin wax, sectioned at 7 μm and stained with haematoxylin and eosin.

The acoustic output of the Duet was characterized using a fibre optic hydrophone (FOPH-500, University of Stuttgart, Germany). Measurements were taken in an acrylic tank with two latex acoustic windows that were coupled to the treatment heads using castor oil. The tank was filled with tap water, degassed overnight with a pinhole degasser. The degasser was run continuously during measurements, and the oxygen content of the water was measured with an oxygen meter (WTW Oxi 330I, Weilheim, Germany). The gas content stabilized at ≈ 2 mg/L (≈ 20% of saturation). For waveform measurements the glass-fibre tip was positioned at the geometric focus of the lithotripter, located using the alignment stylus of the Duet. This position was marked by crossed lasers and used for subsequent measurements. Waveforms were collected using the Fast-Frame setup of a Tektronix (TDS 5034) oscilloscope and post-processed using programs written in LabVIEW (National Instruments, Austin, TX, USA). A photodiode was used to assess the time delay between the firing of the electrodes. The photodiode was positioned closer to one of the treatment heads to distinguish the signal coming from that head.

All measurements were considered numerical variables and summarized as the mean (SEM). Mixed-effect models were used to assess the association of measurements to factors such as lithotripter (Duet vs HM3), treatment (control vs SWs), time (before vs 1 h after SWL), kidney (shocked vs unshocked) and their interactions. Multiple comparisons of means were made by Tukey's adjustment tests; $P < 0.05$ was considered to indicate statistical significance. Pearson correlation coefficients were used to assess the linear

TABLE 1 Basal values of cardiovascular and renal function. Values are mean (SEM)

Group (n)	MAP, mmHg	GFR, mL/min	RPF, mL/min	EPAH, %
Duet lithotripter				
1 – sham (8)	80 (3)	12.8 (1.5)	159 (10)	86 (3)
2 – 2400 SWs (10)	82 (2)	15.7 (1.7)	168 (20)	87 (2)
HM3 lithotripter				
3 – sham (9)	69 (3)	13.6 (1.2)	172 (8)	83 (2)
4 – 2400 SWs (12)	75 (3)	14.1 (1.1)	163 (15)	87 (2)
5 – 4800 SWs (8)	72 (2)	11.0 (1.2)	176 (34)	83 (2)

MAP, mean arterial blood pressure.

TABLE 2 Pearson correlation coefficients (r value) were used to assess the closeness of the linear relationship between values before and after SWL. For a perfect correlation r = 1

Measurement	Lithotripter	N	SW number	r	P
GFR	Duet	10	2400	0.28	0.428
	HM3	12	2400	0.78	0.003
	HM3	8	4800	0.67	0.071
RPF	Duet	10	2400	0.45	0.192
	HM3	12	2400	0.87	0.001
	HM3	8	4800	0.91	0.002

relationship of measurements of the SWL-treated kidney.

RESULTS

Blood pressure and renal function were similar in the two Duet groups and in the three HM3 groups (Table 1). The mean arterial pressure and EPAH were unchanged from baseline after treatment in all groups, except in sham Duet-treated pigs, where there was a decrease of 9 (2) mmHg ($P < 0.05$). The renal haemodynamic responses are shown in Fig. 1.

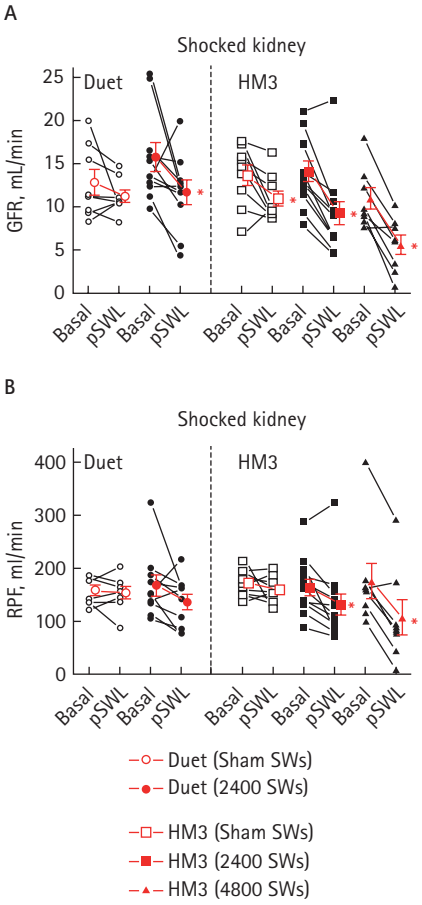
For the Duet, the GFR and RPF remained constant in control pigs. Duet-treated pigs showed a decline in GFR of 4.1 (1.9) mL/min ($P = 0.058$). The RPF declined in eight of 10 pigs, but as a group this was not statistically significant, at 31 (19) mL/min ($P = 0.13$). The contralateral renal filtration and perfusion was unchanged in control pigs, whereas in Duet-treated pigs there was a reduction in GFR of 3.2 (1.2) mL/min ($P < 0.05$) and in RPF in seven of 10 pigs that, as a group, was not statistically significant, at 25 (19) mL/min ($P = 0.22$; not shown).

With the HM3, there was a time-related decline in GFR of 2.6 (1.1) mL/min ($P < 0.05$) in the control pigs, whilst RPF remained unaltered. With 2400 SWs, the GFR decreased by 4.8 (0.8) mL/min and the RPF by 32 (10) mL/min (both $P < 0.01$). With 4800 SWs, the GFR decreased by 5.4 (1.0) mL/min and the RPF by 68 (14) mL/min (both $P < 0.01$). A fall in GFR of 21–34% was still detectable in HM3-treated pigs after factoring the time-related decline in GFR observed in the controls (not shown).

The contralateral kidneys of control pigs had no significant change in GFR or RPF, whereas in pigs given 2400 SWs the GFR decreased by 2.9 (1.0) mL/min ($P < 0.05$) and the RPF by 17 (8) mL/min ($P = 0.053$), with 4800 SWs, the GFR decreased by 3.3 (1.1) mL/min and the RPF by 31 (12) mL/min (both $P < 0.05$; not shown).

Thus, overall, the magnitude of the GFR and RPF response in the shocked kidney was similar in the Duet-treated and HM3-treated pigs. However, HM3-treated pigs had higher (>60%) and significant correlation coefficients for GFR and RPF, whereas there were lower (<50%) and insignificant correlation coefficients in the Duet-treated pigs (Table 2). A higher correlation coefficient indicated that functional changes in GFR and/or RPF were more predictable after SWL.

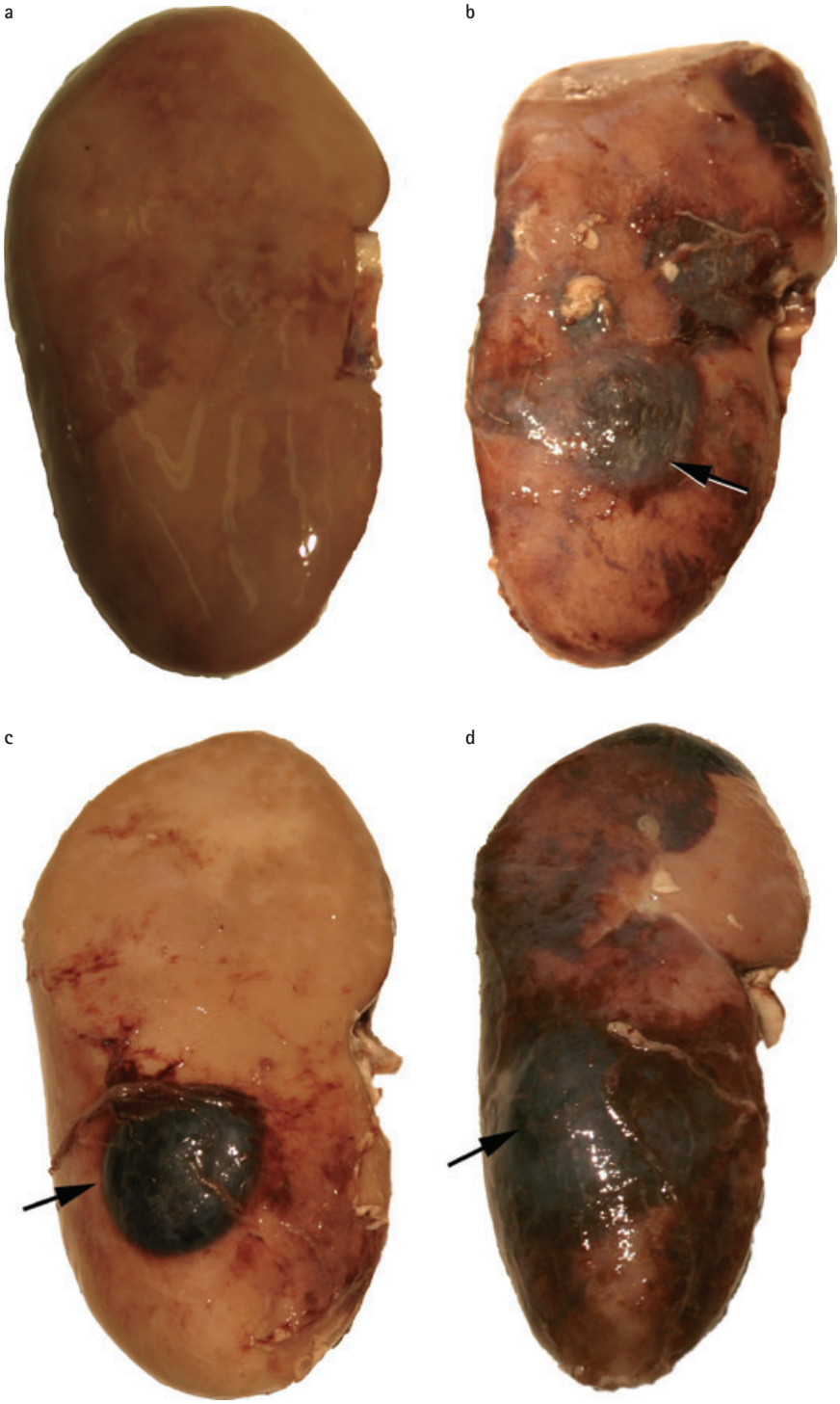
*FIG. 1. Renal filtration and perfusion responses in the SWL-treated kidney. Black lines are individual responses, the mean (SEM) group response is in red. Basal, baseline value; pSWL, 1 h post-treatment (sham or SWL) value, *P < 0.05 vs baseline.*



All kidneys were examined for evidence of subcapsular haemorrhage at autopsy. No sites of haemorrhage were seen on any sham-treated kidneys (Fig. 2a). Two of the 10 Duet-treated kidneys had sites of subcapsular bleeding; one showed several small sites of subcapsular bleeding (not shown) and another showed a well-defined subcapsular haematoma in the targeted pole; nine of the 12 HM3 2400 SW-treated kidneys and five of the eight HM3 4800 SW treated kidneys (Fig. 2b–d) had a subcapsular haematoma in the targeted pole that was always large.

The degree of intraparenchymal haemorrhage induced by the Duet was variable; one pig had no detectable lesion, two had a lesion below the sensitivity of accurate measurement and assigned a threshold value of 0.1% FRV, and one pig had the largest lesion, of 3.16% FRV. The mean (SEM, range) for the eight

FIG. 2. Gross morphology of the kidneys at autopsy. No sites of subcapsular haemorrhage were seen on any sham-treated kidneys (a). Two of the 10 Duet-treated kidneys showed subcapsular bleeding, with one kidney having a well-defined subcapsular haematoma in the targeted pole (arrow, b), while nine of the 12 HM3 2400 SW-treated kidneys (arrow, c) and five of the seven HM3 4800 SW-treated kidneys (arrow, d) had well-defined subcapsular haematomas that were always large. ×1.2 (a–d).



Duet-treated kidneys was 0.96 (0.39, 0–3.16)% FRV. All HM3-treated kidneys had a measurable lesion of 1.08 (0.38, 0.28–2.50)% FRV with 2400 SWs and 2.71 (1.02, 1.55–7.02)% with 4800 SWs (both six kidneys). Figure 3a shows a digitized and colour-coded cross-section from the Duet-treated kidney with no detectable lesion, while Fig. 3b shows a cross-section from the kidney with the largest lesion induced by the Duet (3.16% FRV). Sites of intraparenchymal haemorrhage were seen in the medulla and cortex, a pattern of injury that was similar to kidneys treated with the HM3 at 2400 or 4800 SWs (Fig. 3c,d). Cortical damage with the Duet was mainly to the walls of veins and arteries within the area of the kidney targeted by the focal zone. Damage varied from dissection of the tunica media, including injury to smooth muscle cells (Fig. 4a,b), to rupture of the vessel wall permitting release of blood into the interstitial space. Histopathological examination of damaged papilla from the Duet- and HM3-treated kidneys showed cellular disruption of the vasa recta resulting in intraparenchymal haemorrhage and injury to nearby tubules, with cellular necrosis and tearing of the tubular basement membrane (Fig. 4c,d).

The Duet fired shock pulses from both treatment heads in relatively close synchrony, but with an increase in interpulse delay as the electrodes aged. When firing was precisely synchronous, the resulting waveform had a peak positive pressure of 40–120 MPa, 1–2 μs duration, and a negative pressure trough of ≈ 5 MPa (Fig. 5). The waveform from an individual treatment head had about half this amplitude (Fig. 6). The acoustic output of the individual heads was variable, and the amplitude of the peak positive pressure of consecutive pulses could differ by a factor of two. When timing of the dual pulses was close, but not perfectly synchronous, the waveform had two peaks (Fig. 5). Typically, the second peak was higher, probably due to summation of the acoustic pressures. With an increasing number of shots fired on a set of electrodes, the time delay between the dual pulses increased. A delay of ≈ 3 μs produced two separate waveforms, each typical of the SWs from a single source. The decay in pulse synchrony was documented by recording the interpulse delay using a photodiode. As the number of shots increased, the delay increased (Fig. 7). Synchrony was nearly perfect for the first 500 dual pulses, and over 1000 pulse pairs ≈ 80% were separated by

≈ 2 μs or less. Over the 2400 SWs manufacturer-recommended lifetime of the electrodes, 49% of pulses had a delay of ≤2 μs, and for 14% the delay was ≥7 μs. The last 100 paired pulses showed a mean delay of ≈ 6 μs, and ≈ 80% of these dual pulses were completely separate (>2 μs delay).

DISCUSSION

In the present study, pig kidneys treated with a clinical dose of synchronous SWs from the Duet lithotripter had a relatively small reduction in GFR and renal perfusion. Overall, these responses were similar to those in kidneys exposed to 2400 SWs with the HM3, and slightly less than in kidneys exposed to 4800 SWs. All pigs treated with the Duet or the HM3 showed some decrease in renal function in the untargeted kidneys. This was not unexpected, as SWL of one kidney impairs bilateral renal function in animals [16,19] and humans [20]. The functional response to treatment with the Duet, although similar in magnitude to that with the HM3, was more variable. Pearson correlation coefficients showed a strong linear relationship between the renal haemodynamic responses for both doses of SWs with the HM3 but not with the Duet.

Histological analysis and morphological quantification of the haemorrhagic lesion showed that tissue injury with 2400 paired SWs with the Duet was similar to that produced by 2400 SWs with the HM3. Like the functional response to treatment, morphological damage with the Duet appeared less consistent than that with the HM3. Whereas all HM3-treated kidneys showed visible damage and quantifiable lesions, three of eight kidneys in the Duet-treated group had lesions below the sensitivity of measurement, and in one of these, no lesion was visible.

Thus, by measures of both morphological tissue damage and renal functional response, the injury to pigs treated with synchronous dual SWs was similar to, but more variable than, that in pigs treated with the same number of SWs from a conventional lithotripter. Although this seems an encouraging result, we urge caution in interpreting it. While we gave the same number of SWs with both lithotripters, we cannot conclude that treatment was equivalent. All lithotripters are similar in that

FIG. 3. Digitized and colour-coded cross-sections of Duet-treated and HM3-treated kidneys. The degree of intraparenchymal haemorrhage induced by the Duet lithotripter varied from no detectable lesion in one pig (a) to a lesion size of 3.2% of the FRV (b). The sites of intraparenchymal haemorrhage were noted in the papilla (double arrows) and adjacent cortical tissue (arrow) within the focal zone. All kidneys that received 2400 SWs (c) or 4800 SWs (d) from the HM3 lithotripter had lesions like those in Duet-treated kidneys. Sites of intraparenchymal haemorrhage were seen in the medulla (double arrow) and cortex (arrows). ×1.2 (a–d).

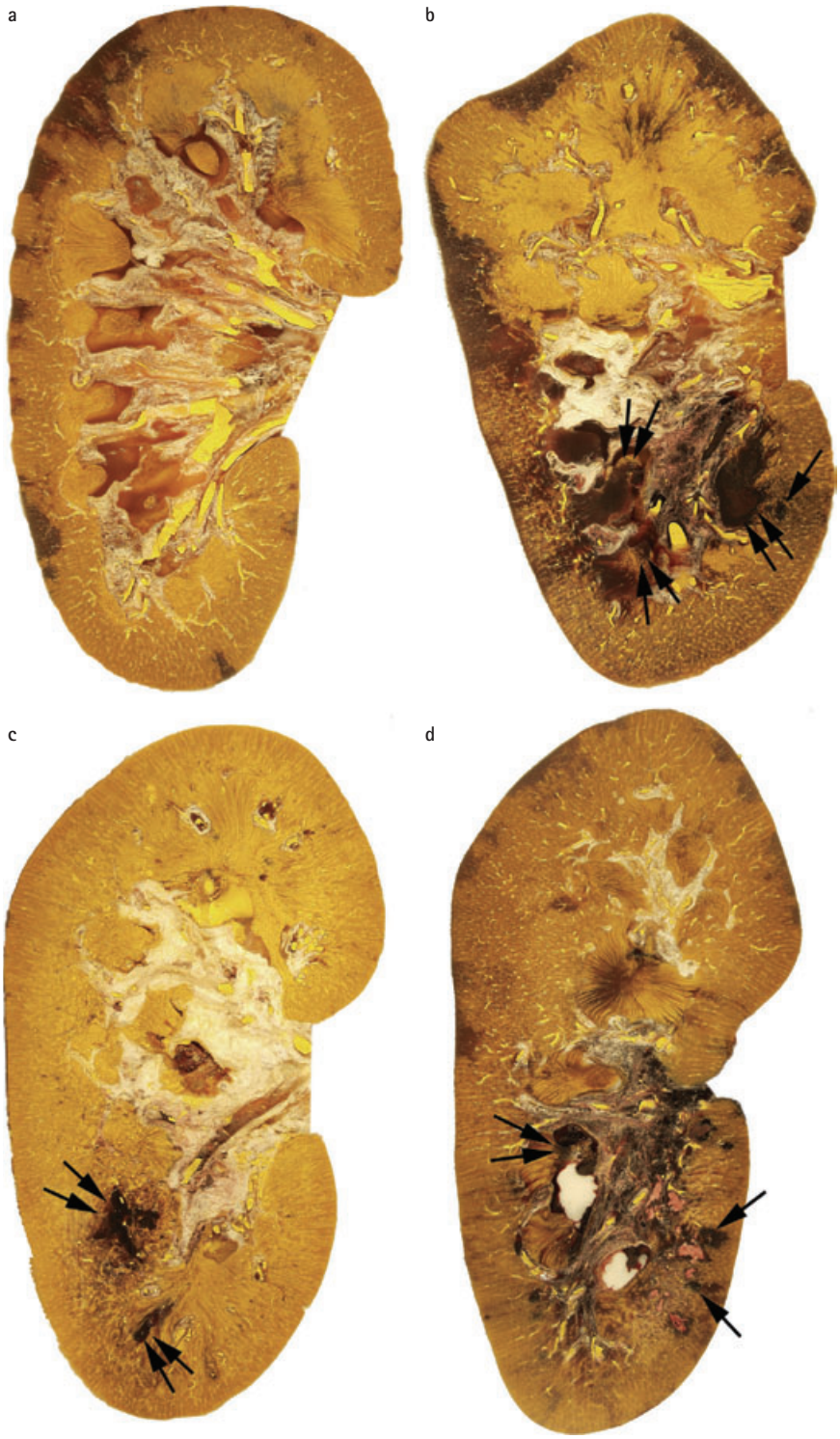


FIG. 4. Histopathological examination of sites of cortical and medullary damage induced by the Duet and HM3 lithotripters. Cortical damage was primarily localized to the walls of veins and arteries within the area targeted by the focal zone, and varied from dissection of the tunica media with blood cells and damaged smooth muscle cells (arrows, a and b) to rupturing of the vessel wall permitting the release of blood into the interstitial space. Histopathological examination of damaged papilla from both the Duet- and HM3-treated kidneys show cellular disruption of vasa recta resulting in intraparenchymal haemorrhage (arrows c) and injury to nearby tubules that included cellular necrosis and tearing of the tubular basement membrane (arrows, d). The pattern of cortical and medullary injury was similar between the two lithotripters. ×1200 (a); ×1000 (b–d).

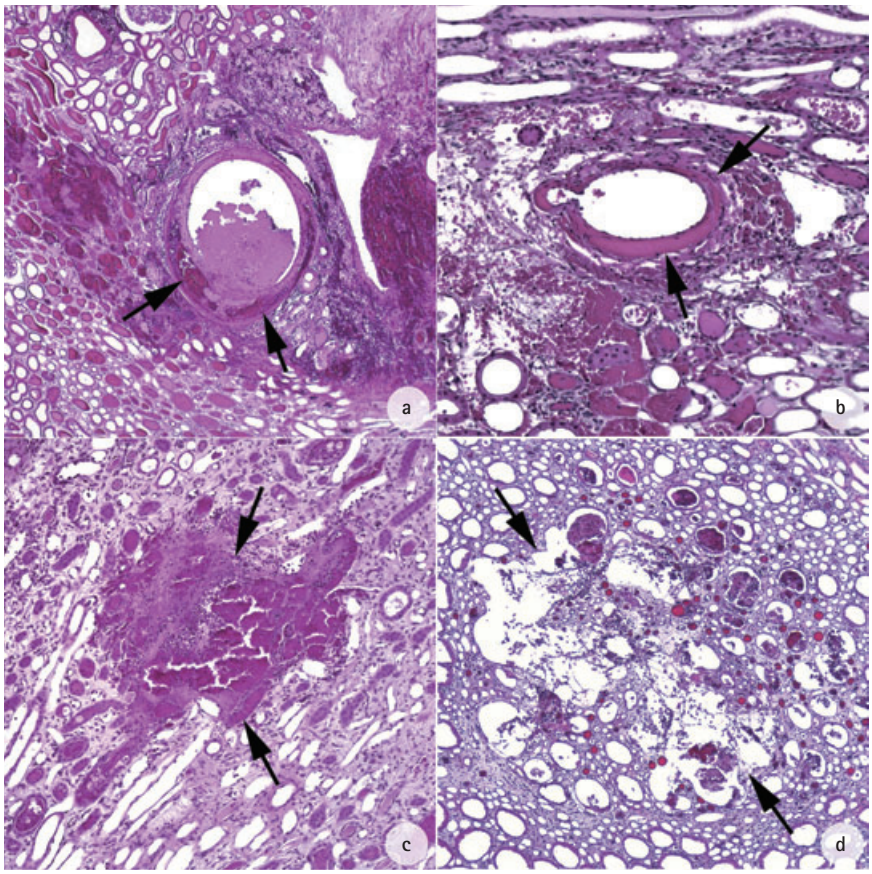
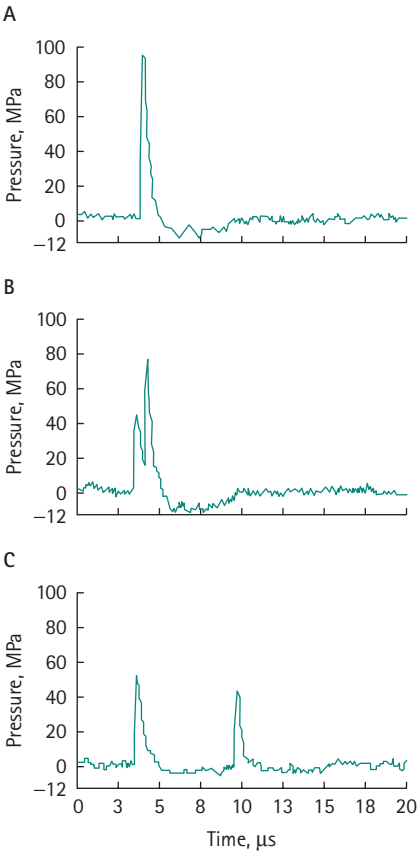


FIG. 5. The effect of interpulse time delay on waveforms from the Duet lithotripter fired at 17 kV. (A) When the two electrodes fired in precise synchrony (with no interpulse delay), acoustic pressures at the focal point of the lithotripter were about twice that produced by one electrode. (B) A slight delay in timing (<1 μs) resulted in two peaks, the second of which was typically higher in amplitude. (C) A longer delay (6 μs) between the firing of the electrodes separated the peaks, which were correspondingly lower in amplitude, and similar to SWs fired from one source.



they produce a signature waveform, but no two lithotripters combine precisely the same shock source and focusing mechanism, and so their acoustic output and the distribution of energy within the focal volume will differ. Different lithotripters generate different acoustic fields even if operated at the same voltage. Also, the dimensions and energy flux densities that characterize the focal volumes of different machines will differ even when they are operated to deliver the same acoustic pressure. Thus, the groups in the present study did not receive equivalent doses of SW energy. However, this comparison is relevant, in that the SW doses delivered with the Duet and the HM3 were typical of those used to treat patients with these lithotripters.

The rationale of using simultaneous SWs from two treatment heads builds on the idea that two relatively low-energy pulses can deliver twice the energy to a common focal volume, i.e. if the pulses are synchronous, their focal volumes will intersect, creating a focal zone of coincidence with features different from that of a single-shock source fired separately. We expected that acoustic pressures within this zone would be additive of the two separate pulses, and this is what we measured. We also expected that the dimensions of the zone of coincidence and the focal zone of a single pulse would differ, but it is difficult to say by how much. Direct mapping of the dual-pulse field in the Duet is made difficult by the great shot-to-shot variability of the pulses. Preliminary results of two-dimensional modelling using values for a single pulse as input data suggest that there will be both constructive and destructive interference as the pulses interact (unpublished, Y.A.P.). If there is a delay between the pulses (if they are not simultaneous) there will be spatial drift in the zone of coincidence, and if the delay is ≥7 μs, the two SWs will miss one another altogether.

There was a degradation in the synchrony of dual pulses with the Duet. Early in the life of electrode pairs, the individual SWs arrive at the hydrophone with little delay between them. However, as the electrodes aged the mean delay between the pulses became

longer. About 95% of the first 500 paired pulses had a delay of ≤2 μs, and of the first 1000 pulses ≈ 80% were within this short delay. Of the remaining 1400 paired pulses of electrode lifetime, only ≈ 27% were simultaneous (≤2 μs delay), and ≈ 25% had a delay of ≥7 μs. Preliminary *in vitro* studies with the Duet suggest that this can have a dramatic effect on the efficiency of stone breakage; stone breakage was more efficient during the first 1000 dual pulses than during the second 1000, and when pulse timing is manipulated to give a 10-μs delay, breakage is significantly less efficient than with pulses delivered by a one shock-head alone [21].

A delay between dual pulses means that they will not arrive at the geometric focus of the lithotripter at precisely the same time, but does not mean that they will not intersect elsewhere. A lithotripter SW advances at ≈ 1.5 mm/μs. As the shock heads of the Duet are at an angle of 72°, a delay of 6 μs will shift the point of coincidence by ≈ 8.6 mm, i.e. move the axis of the focal zone by nearly 1 cm. Many SW pairs were separated by such a delay, and for some the delay was as much as ≈ 16 μs, for which the displacement of the focal axis would be substantial (≈ 1.5 cm). Considering the variability in pulse delay over the lifetime of the electrodes, it is clear that the focal zone could not have stayed within just one region of the kidney. This shift in targeting might have been a factor in the variability in functional response and tissue damage in Duet-treated pigs.

Movement of the focal zone might also have affected the severity of morphological damage. In studies with the HM3, we found that SW damage was relatively consistent and that the lesion was focal [8,22]. There can be visible damage outside the targeted region, but quantifiable injury is typically limited to one area of tissue. We previously showed that injury with the HM3 increases from ≈ 0.2% FRV at 1000 SWs, to ≈ 6.1% FRV at 2000 SWs [16,23]. Thus, the vast majority of measurable damage occurs after 1000 SWs. It seems likely that a threshold exists for significant haemorrhagic injury with the HM3, and that it exceeds 1000 SWs. It also seems likely that, if targeting were to be shifted before the threshold was reached, tissue damage would be less. This could be the case during treatment with the Duet in synchronous mode, i.e. repetitive sets of simultaneous paired SWs would be expected to hit the same area of the kidney. As synchrony degrades and targeting becomes less consistent, sequential SW pairs no longer impact the same region of tissue, and it takes more SWs to reach the threshold for significant haemorrhagic injury. This suggests that if more of the dual SWs had been truly simultaneous, damage to the kidney would have been more severe.

FIG. 6. Acoustic output for a single-shock source of the Duet lithotripter fired at 17 kV, 1 Hz. Shown here are waveforms for two shock pulses showing the variability in output from a single-shock source (bottom head) in the Duet. SW 210 had low amplitude (≈ 20 MPa peak P^+) and relatively long pulse duration (≈ 2 μs), while SW 200 was high amplitude (≈ 70 MPa peak P^+) and shorter duration (≈ 1 μs). Also shown is the mean of values over the recommended lifetime (2400 SWs) of the electrode (30 MPa P^+, duration 1.5 μs, ≈ 5 MPa P^-).

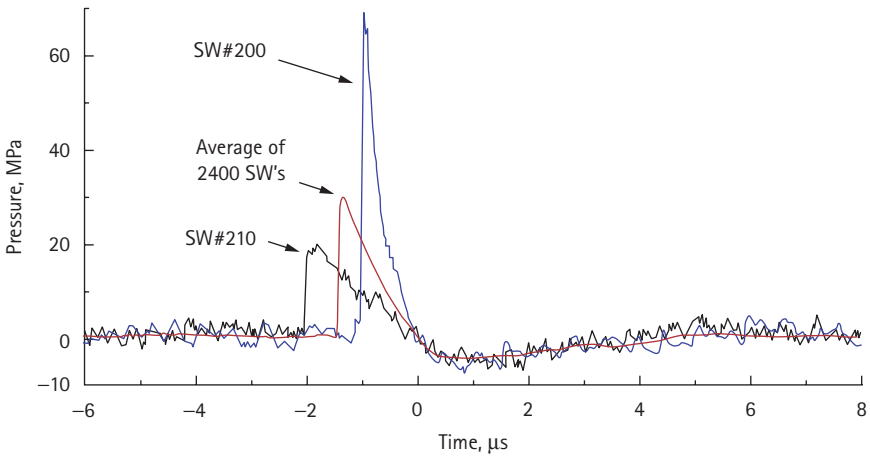
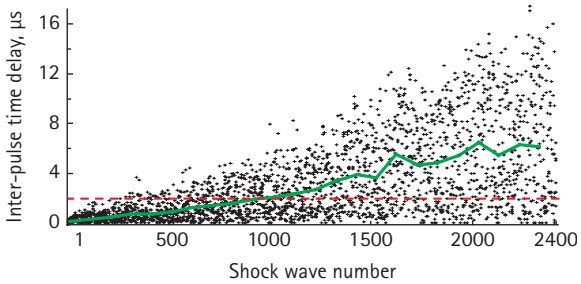


FIG. 7. Photodiode measures of interpulse delay for a set of Duet electrodes fired in synchronous mode. Early in the life of the electrodes, firing was nearly simultaneous and most of paired pulses were separated by a delay of ≤ 2 μs (dashed line). As the electrodes aged, the interpulse delay increased, such that during the last 1400 paired pulses only ≈ 27% were simultaneous (≤ 2 μs). Solid line tracks mean interpulse delay at 100-shot intervals.



Acoustic coupling could also have contributed to the variability in response in Duet-treated pigs. Recent *in vitro* studies showed that the coupling interface of dry-head lithotripters is prone to catching air pockets that can have a significant effect on the transmission of SW energy [24]. Air pockets occur even under controlled *in vitro* conditions, and the quality of the interface can differ markedly from one coupling to the next [25]. Clearly the potential for ineffective coupling is a problem common to all dry-head machines, but there might be additional difficulty in maintaining adequate coupling when using lithotripters with two treatment heads.

Another dual-head lithotripter has been used in clinical practice. This (TwinHeads, FMD Corp., Lorton, VA, USA: US Patent 6780161) uses two electrohydraulic shock sources, one in a fixed position under the treatment table, the other movable. Although several reports describe *in vitro* stone breakage, assessment

of renal injury and initial clinical experience with this lithotripter operated in synchronous (simultaneous) mode [26–29], the manufacturer recently disclosed that that dual pulses with the TwinHeads are actually separated by a lengthy delay (≈ 23 ms). The influence of pulse timing on stone breakage and tissue injury in dual-head lithotripsy has yet to be adequately defined, and a certain delay time might be advantageous, but this needs to be determined with rigorous systematic testing.

In conclusion, the present study shows that a clinical dose of paired SWs delivered to the pig kidney with a dual-head electrohydraulic lithotripter (Duet) operated in synchronous mode elicits a renal response similar to, but more variable than, that in the same animal model treated with SWs from a conventional electrohydraulic lithotripter (unmodified Dornier HM3). However, the timing of dual pulses degrades as the electrodes age, affecting targeting of the focal volume and altering the distribution of SW energy, conditions that will reduce the energy flux density of SW exposure to the kidney.

As synchronous pulse delivery (simultaneous pulses from both heads) is just one option with dual-treatment heads, there is a need to assess stone breakage and the renal response to SW delivery in the alternating mode. Also, as previous experiments with dual-shock heads, and complementary studies of tandem SWs delivered along one treatment path, suggest that pulse timing can be used to enhance stone breakage and minimize tissue injury, more studies to assess the potential advantages of pulse timing in dual-head lithotripsy are warranted.

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CONFLICT OF INTEREST

J. Lingeman is a consultant/advisor for Olympus and Lumenis; has an investment interest and is an Officer of General Partner Entity for Midstate Mobile Lithotripsy, LP and Midwest Mobile Lithotripsy, LP; is a meeting participant or lecturer for Storz Medical, Boston Scientific and Lumenis; is taking part in a scientific study or trial for Boston Scientific and receives royalties from Cook Urological. He has also been a consultant/advisor, meeting participant or lecturer and has taken part in a scientific study or trial for Thermatrix; he has also had an investment interest and has been an Officer of General Partner Entity for Progressive Thermotherapy, LP. Source of funding: National Institute of Health Grants DK43881 and DK55674.

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Abbreviations: **SW(L)**, shock-wave (lithotripsy); **FDA**, US Food and Drug Administration; **PAH**, para-aminohippuric acid; **EPAH**, renal extraction of PAH; **GFR**, glomerular filtration rate; **RPF**, renal plasma flow; **FRV**, functional renal volume; **F2**, second focal point.