Effects of Lithotripter Fields on Biological Tissues

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Abstract: Biological effects resulting from exposure to lithotripter fields include hemorrhage in soft tissues, such as the kidney, lung and intestine, the production of premature cardiac contractions, malformations in the chicken embryo and killing of Drosophila larvae. Pulsed ultrasound can produce similar bioeffects at comparable pressure thresholds. Tissues that contain gas bodies, either naturally or after the addition of ultrasound contrast agents, are particularly susceptible to damage from low amplitude lithotripter fields. Lung and intestine contain gas naturally and are hemorraged by exposure to lithotripter fields on the order of 1 MPa. After the introduction of an ultrasound contrast agent into the vasculature, many organs and tissues, such as the bladder, kidney, fat, muscle and mesentery, show extensive hemorrhage after exposure to lithotripter pressures less than 2 MPa. Tissues near developing bone are also selectively susceptible to damage from exposure to low amplitude lithotripter fields. The thresholds for hemorrhage in tissues near developing bone, such as the fetal head, limbs and ribs, are all less than 1 MPa for exposures with a piezoelectric lithotripter. Cavitation and purely mechanical forces have been investigated as possible mechanisms for these biological effects of lithotripter fields.

Lithotripsy has become a common procedure for the treatment of kidney stones. In addition to stone disintegration, though, lithotripter fields are capable of producing biological effects. Bioeffects resulting from exposure to lithotripter fields include hemorrhage in soft tissues, such as the kidney (1), lung (2) and intestine (3,4), the production of premature cardiac contractions (5), malformations in the chicken embryo and killing of fruit fly larvae. Since heat production is minimized by the low temporal average intensities associated with lithotripter fields, lithotripsy provides unique opportunities for studying non-thermal mechanisms for biological effects of ultrasound. Lithotripter studies, combined with studies of bioeffects of pulsed ultrasound and contrast agents, provide insight to the bioeffects of cavitation in vivo.

Tissues known to contain gas bodies are particularly susceptible to damage from exposure to lithotripter and pulsed ultrasound fields. Lung and intestine contain gas bodies naturally and both are hemorrhaged from exposure to low amplitude lithotripter fields and pulsed ultrasound. The threshold for lung hemorrhage with 20 pulses from a spherically diverging spark source lithotripter is \( \sim 1.5 \) MPa and negative pressure pulses produce no greater damage than positive pressure pulses (2). Studies with pulsed ultrasound indicate the threshold for lung hemorrhage is weakly dependent upon frequency and that the addition of cavitation nuclei into the vasculature does not increase the extent of lung hemorrhage. The threshold for intestinal hemorrhage with 200 pulses from a piezoelectric lithotripter is 1–3 MPa (3). In contrast with lung hemorrhage, though, negative pressure lithotripter pulses produce more intestinal hemorrhage than positive pressure pulses. The threshold for intestinal hemorrhage from exposure to pulsed ultrasound is strongly dependent upon frequency.

In addition to tissues that contain gas bodies naturally, tissues containing gas-based ultrasound contrast agents are also susceptible to damage from exposure to lithotripter fields. Recent studies investigated the effects of low amplitude lithotripter fields on tissues containing contrast agents in vivo (6,7). The abdominal regions of mice were exposed to 200 pulses from a piezoelectric lithotripter with peak amplitude of only 2 MPa. At four intervals during the exposure, mice were injected with Albunex\textsuperscript{TM} for a total of \( \sim 0.1 \) mL of the contrast agent. Mice exposed to the lithotripter field alone (w/o ultrasound contrast injection) showed only minor hemorrhage to the lung and intestine consistent with earlier studies. In comparison, mice injected with Albunex\textsuperscript{TM} during exposure showed extensive hemorrhage to the intestine, kidney, muscle, mesentery, stomach, bladder, seminal vesicle and fat (6).

Although Albunex\textsuperscript{TM} is effective as a contrast agent for diagnostic imaging in vivo for only a few minutes, Albunex\textsuperscript{TM} continues to enhance hemorrhage produced by lithotripter exposure for hours after injection (7). Mice received a single injection of 0.1 mL Albunex\textsuperscript{TM} and then were exposed to 200 lithotripter pulses at times ranging from 5 min to 24 hr after injection. For exposures at low amplitude (2 MPa), tissues such as the bladder, mesentery...
and intestine continued to be susceptible to damage for times as long as 4 hr after injection. For exposures at clinical lithotripsy amplitudes (60 MPa), Albunex™ continued to enhance hemorrhage in the bladder, muscle and seminal vesicle when exposures were performed up to 6 hr after injection. Albunex™ did not enhance the extent of hemorrhage in any of the tissues investigated when exposures at 60 MPa were performed at 24 hr after injection.

Recent studies have determined that low amplitude lithotripter fields can produce hemorrhage near developing bone in the late-gestation murine fetus (4,8). Pregnant mice were exposed on the 18th day of gestation to 200 pulses from a piezoelectric lithotripter at axial, peak positive pressures ranging from 0–10 MPa. Immediately following exposure, dams were cervically dislocated and fetuses were observed for hemorrhage to various tissues. Damage was typically associated with tissues near developing bone and cartilage such as the head, limbs and ribs. In contrast, soft tissues distant from bone, such as the liver, intestine and stomach, were free of hemorrhage. The head was the site at which hemorrhages occurred most often and at the lowest pressure amplitudes. Hemorrhages in the limbs were seen at the ends of the long bones and in the metacarpal and metatarsal areas. Thresholds for hemorrhage in tissues near fetal head, limbs and ribs are all less than 1 MPa (8). Pulsed ultrasound can also produce hemorrhage in the late-gestation fetal mouse. At 1 MHz (10 μs pulse; 100 Hz PRF), the threshold for hemorrhage to the head is ~5 MPa peak positive pressure and the threshold increases with increasing frequency. Hemorrhages, similar to those reported for late-gestation fetal mice exposed to lithotripter and pulsed ultrasound fields, have also been observed in neonatal mice for comparable exposures.

In the late-term fetus, hemorrhages from lithotripter fields are always associated with tissues near developing bone or cartilage. The association of hemorrhage with developing bone was tested by exposing fetuses at 9 days of gestation when there is no development of skeletal modeling in the fetal mouse. Essentially no fetal hemorrhages were observed when pregnant mice at 9 days of gestation were exposed to lithotripter fields at 10 MPa. Since bone is not known to selectively contain cavitation nuclei, the observation of hemorrhage in tissues near developing bone suggests a purely mechanical mechanism for this biological effect.

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REFERENCES


