Robotically Assisted Sonic Therapy as a Noninvasive Nonthermal Ablation Modality: Proof of Concept in a Porcine Liver Model

Amanda R. Smolock, MD, PhD
Mircea M. Cristescu, MD, MBA
Eli Vlaisavljevich, PhD
Annette Gendron-Fitzpatrick, DVM, PhD
Chelsey Green, BS
Jonathan Cannata, PhD
Timothy J. Ziemlewicz, MD
Fred T. Lee, Jr, MD

Purpose:
To determine the feasibility of creating a clinically relevant hepatic ablation (ie, an ablation zone capable of treating a 2-cm liver tumor) by using robotically assisted sonic therapy (RAST), a noninvasive and nonthermal focused ultrasound therapy based on histotripsy.

Materials and Methods:
This study was approved by the institutional animal use and care committee. Ten female pigs were treated with RAST in a single session with a prescribed 3-cm spherical treatment region and immediately underwent abdominal magnetic resonance (MR) imaging. Three pigs (acute group) were sacrificed immediately following MR imaging. Seven pigs (chronic group) were survived for approximately 4 weeks and were reimaged with MR imaging immediately before sacrifice. Animals underwent necropsy and harvesting of the liver for histologic evaluation of the ablation zone. RAST ablations were performed with a 700-kHz therapy transducer. Student t tests were performed to compare prescribed versus achieved ablation diameter, difference of sphericity from 1, and change in ablation zone volume from acute to chronic imaging.

Results:
Ablation zones had a sphericity index of 0.99 ± 0.01 (standard deviation) ($P < .001$ vs sphericity index of 1). Anteroposterior and transverse dimensions were not significantly different from prescribed (3.4 ± 0.7; $P = .08$ and 3.2 ± 0.8; $P = .29$, respectively). The craniocaudal dimension was significantly larger than prescribed (3.8 ± 1.1; $P = .04$), likely because of respiratory motion. The central ablation zone demonstrated complete cell destruction and a zone of partial necrosis. A fibrous capsule surrounded the ablation zone by 4 weeks. On 4-week follow-up images, ablation zone volumes decreased by 64% ($P < .001$).

Conclusion:
RAST is capable of producing clinically relevant ablation zones in a noninvasive manner in a porcine model.
Thermal ablation modalities are percutaneous methods that require precise applicator placement in the targeted tissue (1). There is no intrinsic control of the ablation zone other than varying the duration and amplitude of the power applied to the applicator, limiting use in certain critical anatomic areas such as parenchyma adjacent to bile ducts and bowel (2–4). All thermal ablation zones are surrounded by a 3–8-mm zone of partial ablation where tissue is exposed to sublethal temperatures of 40°–45°C resulting in incomplete cell death, which may stimulate local and systemic tumor growth (5,6). Although percutaneous techniques are well established and minimally invasive, complications related to puncture sites (ie, hemorrhage, pneumothorax), limitations in the ability to access and ablate certain anatomic areas (ie, hepatic dome, caudate), technical challenges of precisely placing applicators, and limitations and complications of anesthesia are some of the challenges of percutaneous approaches (7–9).

Histotripsy is a nonthermal, noninvasive ultrasonic ablation method that controllably fractionates soft tissues into an acellular homogenate through the precise control of acoustic cavitation generated by high-pressure (>10 MPa), short-duration (<20 μsec) ultrasound pulses at low duty cycles (<1%) (10–13). Importantly, histotripsy is not thermal high-intensity focused ultrasound, or HIFU, which uses lower-amplitude, near-continuous pulses to create heat at the focal zone (14). Histotripsy has been shown capable of creating precise hepatic ablations without recognizable cellular structures while preserving large vessel integrity (15–17). A recent survival rodent study also demonstrated that histotripsy liver lesions were rapidly resorbed over approximately 28 days (18). The high peak negative pressure used in histotripsy generates microbubbles in tissue that can be visualized under real-time ultrasonography (US), leading to precise targeting (15). Histotripsy delivered by using a robotic arm positioning under software control is termed robotically assisted sonic therapy (RAST).

To date, RAST has not been applied to the liver for ablation volumes of a clinically relevant size or shape that would be typically used for ablation of a human liver tumor (ie, a 2-cm tumor treated with a 5-mm concentric margin). Studies performed in large animal models were acute studies of histotripsy ablations without follow-up. Furthermore, the in vivo imaging appearance of both acute and chronic RAST ablations has not been studied, particularly with a clinical magnetic resonance (MR) system (15). The purpose of our study was to determine the feasibility of creating spherical 3-cm RAST ablations in pigs in the acute setting and in those pigs allowed to survive 4 weeks with MR imaging and histopathologic correlation.

Materials and Methods

Our study was supported by HistoSonics (Ann Arbor, Mich) through use of equipment and funding. Authors (A.S., M.C., A.G.F., C.G., T.Z.) not employed by or consultants for HistoSonics had control of inclusion of data presented in this article.

Experimental Design

Our study was performed with approval from our institutional animal care and use committee and was in compliance with National Research Council guidelines (1). Ten female pigs were divided into two groups: acute (n = 3) and chronic (n = 7) (Fig 1). Pigs in the acute group underwent treatment with RAST, MR imaging, and immediate sacrifice and necropsy. Pigs in the chronic group underwent RAST followed by MR imaging, survival for 25–30 days, reimaging with MR imaging, and subsequent sacrifice and necropsy. The liver and relevant adjacent organs were inspected for gross signs of damage and harvested for histopathologic evaluation.

Animal Handling and Anesthesia

Female pigs (mean weight ± standard deviation, 70 kg ± 10; Arlington Farms, Arlington, Wis) were sedated by using an intramuscular injection of tiletamine and zolazepam (Telazol; Zoetis, Kalamazoo, Mich), atropine (Phoenix Pharmaceutical, St. Joseph, Mo), and xylazine (AnaSed; Lloyd, Shenandoah, Iowa). The animals were intubated and anesthesia was maintained with inhaled isoflurane (Halocarbon Laboratories, River Edge, NJ) during mechanical ventilation. Intravenous fluids were administered through an auricular vein. Animals were euthanized by using an intravenous injection of pentobarbital sodium and phenytoin sodium (Beuthanasia-D; Schering-Plough, Kenilworth, NJ).

Prior to treatment, all pigs received a single oral dose of 325 mg aspirin and a single intramuscular injection of 40 mg enoxaparin.

RAST Ablations

All ablations were performed with a cart-based therapy system (VortxRx; HistoSonics) with a therapeutic ultrasound signal generator and amplifier and embedded diagnostic ultrasound system. Therapeutic ultrasound was

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Implication for Patient Care

- Robotically assisted sonic therapy has the potential for future use in hepatic ablations.
EXPERIMENTAL STUDIES: Robotically Assisted Sonic Therapy as a Noninvasive Nonthermal Ablation Modality

Smolock et al

in phase at a pulse repetition frequency of 300 Hz and an estimated in situ peak negative pressure greater than 14 MPa. Interleaved lower-amplitude pulses were applied between each therapy pulse as part of the therapy protocol to enhance therapy efficiency (19). The focal spot size was approximately 10 mm in length by 5 mm in diameter. The procedure was completed when all points within the prescribed treatment volume were treated. The treatment bubble cloud was visualized by using B-mode US imaging. Technical success was defined as a clearly visualized bubble cloud throughout the entirety of treatment. All treatments were performed by two resident radiologists (A.S., M.C., each with 4 years of ablation experience) and two faculty radiologists (T.Z., F.L., with 10 years and 20 years of ablation experience, respectively).

MR Imaging

All imaging was performed with a 3.0-T MR imager (Discovery MR750 or MR750w; GE Healthcare, Waukesha, Wis) by using a dedicated body surface coil. A dose (0.05 mmol/kg of body weight) of gadoxetate disodium was intravenously injected at a rate of 2 mL/sec. A localizing sequence, coronal single-shot fast spin-echo sequence, axial T2-weighted fat-suppressed fast spin-echo sequence, diffusion-weighted sequence, and axial T1-weighted gradient-recalled echo sequence were performed. Axial T1-weighted gradient-recalled echo sequences were performed before and after contrast enhancement in the arterial, portal venous, and hepatobiliary phases.

Imaging Data Acquisition

Ablation diameter was measured in three orthogonal planes at MR imaging. The volume of the ablation zone at MR imaging was calculated by using a dedicated volume-rendering software (Vitrea; Vital Images, Minnetonka, Minn). Adjacent organs and structures were visually assessed at MR imaging for complications in consensus by two radiology residents (A.S., M.C.) and two abdominal radiologists (T.Z., F.L.).

Figure 1: Flowchart shows experimental design. MRI = magnetic resonance imaging.

Figure 2: Images show robotically assisted sonic therapy system. A, Coaxially aligned therapy and imaging transducers are mounted on robotic arm next to imaging output and control screens. B, Coaxially aligned ultrasound transducers are placed in water bath overlying abdomen for transcutaneous approach to targeted treatment area.

A proprietary software package was used to plan and deliver a 3-cm spherical treatment. The software controls the robotic micropositioning motors, which move the mounted therapy transducer to deliver the prescribed treatment.

Treatments were performed in the medial lobes of the porcine liver dome near the gallbladder. Histotripsy was performed by using four-cycle pulses (<1% duty cycle) delivered by exciting all elements of the therapy transducer generated with a custom 700-kHz, 20-cm-diameter, 18-element histotripsy therapy transducer. A 3-MHz curvilinear array ultrasonic imaging probe (Model C5–2; Analogic, Peabody, Mass) was coaxially aligned with the therapy transducer to allow real-time image guidance (Fig 2). The therapeutic and diagnostic transducers were mounted along three orthogonal axes to a robotic micropositioning assembly on the end of an articulating arm that can move 3.5 cm in each direction.
Pathologic and Histologic Analysis
Livers were collected immediately after euthanasia, rinsed, and placed in 10% buffered formalin. Livers were sliced along an axial plane similar to that of the MR imaging performed just prior to sacrifice. Ablation zones and the immediately adjacent hepatic tissue were sliced and placed in cassettes. Tissue slices were cut at 6 μm with a Leica RM2235 microtome (Buffalo Grove, Ill). Slides were stained with hematoxylin-eosin, Masson trichrome, and/or van Gieson stains. Slides were then coverslipped and submitted for pathologic analysis by a veterinary pathologist (A.G.F., with 40 years of veterinary pathology experience).

Data Analysis and Statistics
Data analysis was performed by using R version 3.3.2 software (R Foundation for Statistical Computing, Vienna, Austria; available at https://www.r-project.org). Data are presented as means ± standard deviation. Student two-tailed t tests were used to compare prescheduled with observed diameter and volume, and a one-tailed t test was used for testing approximated sphericity against 1. A paired Student two-tailed t test was used to compare MR imaging–determined volumes for those pigs that were followed for 4 weeks with immediate MR imaging–determined volumes. The Shapiro–Wilk test for all variables yielded P values > .05, indicating no strong evidence of nonnormality. An analysis of variance blocked on treatment area was performed to compare diameter sizes within a treatment area. Power was calculated by using the power.t.test function in R with an assumption of α of .05 and effect size defined by Cohen. Power analysis calculated a low chance of detecting small effects. For a sample size of 10, power analysis calculated a 29% chance of identifying a small effect (d = 0.5), 62% chance of detecting a medium effect (d = 0.8), and 80% chance of identifying a large effect (d = 1). For a sample size of six, power analysis calculated a 17% chance of identifying a small effect (d = 0.5), 36% chance of identifying a medium effect (d = 0.8), 51% chance of identifying a large effect (d = 1), and 97% chance of identifying a huge effect (d = 2).

The sphericity (Ψ) was approximated from the three orthogonal measurements by assuming the ablation zone was a prolate or oblate spheroid, depending on whether the middle measurement value was closer to the maximum or minimum measurement. We used the sphericity equation: \[
\Psi = \frac{1}{\pi^3} \frac{(6V)^{2/3}}{\text{SA}},
\]
where V is volume and SA is surface area. V and SA are approximated from the equatorial radius and the polar radius. The average of the more similar measurements was used as the equatorial radius and the most extreme measurement was used as the polar radius.

Results
Animal Treatment and Survival
All ablations were performed in 24 minutes 15 seconds. Animals tolerated the procedure without physiologic indication of stress. The subjects in the chronic study group were awakened from general anesthesia without complication and were monitored daily in the animal care facility with no apparent signs of distress or discomfort. One animal was sacrificed immediately after ablation because of an unintended large body wall injury that occurred secondary to operator error (proceeding with treatment without clearly visualizing the bubble cloud, which resulted in a mistargeted administration). One pig was sacrificed 2 weeks after ablation because of an unrelated infectious enteritis acquired at the animal holding facility.

Technical success.—Technical success rate was 70%. In two cases, the bubble cloud was not well visualized at the initiation of treatment, with improved visualization after treatment was underway. One of these two cases was associated with a minor body wall injury. In another case, the bubble cloud was never clearly visualized throughout the duration of treatment, and a large body wall injury occurred. In all three cases of body wall injury, the acoustic window was substantially blocked by structures such as ribs or stomach, requiring higher emitted pressures to generate a bubble cloud. This also resulted in an increase in acoustic energy deposition to the tissue directly overlying those structures and likely caused the observed body wall injuries.

Ablation Zone
US and MR imaging appearance.—The treatment was visible under real-time US imaging at the targeted area as an echogenic bubble cloud (Figs 3 and 4, A). At MR imaging immediately after ablation (Fig 4, B and C), ablation zones were near spherical in shape and well demarcated from surrounding liver. The ablation zones demonstrated heterogeneous T1 and T2 signal and were without contrast enhancement, surrounding hyperemia, or diffusion restriction both acutely and at 4-week follow-up.

Size and volume.—Mean ablation diameter was 3.5 cm ± 0.8 (Table 1). The anteroposterior and transverse average measurements were not significantly different from prescribed (3.4 ± 0.7; P = .08; 95% confidence interval [CI]: 2.9, 3.9 and 3.2 ± 0.7; P = .29; 95% CI: 2.8, 3.7, respectively), but the craniocaudal measurement was significantly greater (3.8 ± 1.1; P = .04; 95% CI: 3.0, 4.6) (Table 1). The dimensions within a single treatment area, however, were not significantly different from one another (P = .09). The approximated sphericity values for acute ablations were high (0.99 ± 0.01) but significantly lower than 1 (P < .001; 95% CI: 0.98, 0.99) (Table 1). Observed ablation volumes were significantly different from the prescribed 14 mL (25.7 ± 10.8; P = .008; 95% CI: 17.9, 33.5). Ablation volume significantly decreased over time between scans immediately after the procedure and at 4-week follow-up by a mean of 63.9% ± 13.5 (P < .001) (Table 2).

Histologic analysis.—Histologic analysis in acute cases (Fig 4, D–G) demonstrated a central necrotic zone of acellular material surrounded peripherally
EXPERIMENTAL STUDIES: Robotically Assisted Sonic Therapy as a Noninvasive Nonthermal Ablation Modality

Smolock et al.

Demonstrated a central area of necrosis surrounded peripherally by a fibrous capsule consisting of interweaving bundles of fibrous connective tissue (Fig 5, G) and multinucleated macrophages (not pictured). Variably at the periphery was intact except in areas of relative ischemia caused by portal and hepatic vein thrombosis where there were findings of hemorrhagic infarct.

The histologic analysis in animals that survived 4 weeks (Fig 5) demonstrated a central area of necrosis surrounded peripherally by a fibrous capsule consisting of interweaving bundles of fibrous connective tissue (Fig 5, G) and multinucleated macrophages (not pictured). Variably at the periphery was intact except in areas of relative ischemia caused by portal and hepatic vein thrombosis where there were findings of hemorrhagic infarct.

Figure 3

A, US image shows placement of crosshairs and planned treatment volume boundaries at targeted tissue region before initiating treatment. B, During treatment, treatment focal zone is visualized as echogenic bubble cloud (arrowhead). C, Following treatment, ablation zone is seen as anechoic region (arrow).

Figure 4

A, Real-time US image shows echogenic bubble cloud at area of tissue targeted by crosshairs. B, Axial MR image obtained after contrast enhancement shows well-circumscribed ablation closely matching planned size and volume with small perfusion defect related to portal vein thrombosis. C, Three-dimensional surface volume rendering demonstrates nearly spherical ablation zone. D, Image shows that gross pathologic characteristics closely correlate with MR imaging findings. Histologic images demonstrate, E, preserved hepatic architecture outside of ablation with, F, complete cell destruction within ablation and, G, small islands of viable hepatocytes at boundary (arrow). (Hematoxylin-eosin stain; original magnification, ×10.)
of the ablation zone adjacent to the fibrous capsule, there were hepatocytes of indeterminate viability, suggesting incorporation of the acute zone of partial necrosis. Liver lobules immediately outside the capsule varied widely in size and shape, likely an attempt at repair from ischemic injury.

**Imaging Assessment of Adjacent Organs and Structures**

**Body wall.**—Three cases of body wall injuries occurred in the acute animal studies and one case in the chronic animal study group. Nonvisualization of the bubble cloud resulted in a substantial body wall injury in one case, and the animal was therefore immediately sacrificed. Acute histologic analysis from the small body wall injuries demonstrated edema and muscle fragmentation. In one of the small body wall injuries, the animal was allowed to survive for 1 month without apparent distress (Fig 6). Follow-up in this animal demonstrated a persistent body wall injury at MR imaging with high T2 signal and a peripheral rim of enhancement (Fig 6), which at histologic analysis demonstrated muscle necrosis and fibrosis surrounded by infiltrating inflammatory cells.

**Vessels and bile ducts.**—Portal and hepatic venous thrombosis was encountered in the immediate period after ablation. Nine of 10 treatments (three acute, six chronic) were associated with portal venous thrombosis, and two of 10 treatments (one acute, one chronic) demonstrated hepatic venous thrombosis (Table 3). Four of nine portal venous thromboses and one of two hepatic venous thromboses were completely occlusive. Thrombosis involved branch vessels only near the ablation zone in four of the nine portal vein thromboses and one of the two hepatic vein thromboses. In the other instances, clot propagated centrally to central and/or lobar portal or hepatic veins. Clot burden in all cases was improved or near completely resolved on follow-up images at 4 weeks (Fig 5). No major bile duct injuries, stenoses, or occlusions outside of the ablation zone were observed. In two cases, patent and unaltered bile ducts were visualized traversing the ablation zone on delayed gadoxetate disodium–enhanced hepatobiliary phase images (Fig 7).

**Adjacent organs.**—Surrounding organs and tissue were evaluated at MR imaging and inspected during necropsy for signs of injury or damage. No apparent injuries were observed to adjacent organs such as stomach, large bowel, small bowel, or gallbladder.

**Discussion**

Histotripsy is a nonthermal and noninvasive ablation method that uses focused ultrasound to generate acoustic cavitation at a focal point to destroy tissue (10–13). When combined with robotic assistance and software planning, the technique is referred to as robotically assisted sonic therapy or RAST. Small histotripsy ablations have been created in an in vivo porcine liver model (15). However, larger clinically relevant ablations, longitudinal assessment in a survival animal model, and in vivo imaging with a clinical MR imaging system have not previously been studied. The results of our study demonstrate that RAST can rapidly produce clinically useful ablation zones that adhere closely to the prescribed size and shape and are not associated with any substantial complications. The targeted tissue was completely destroyed into an acellular homogenate surrounded by only a narrow zone of partial necrosis, demonstrating the precision of RAST. In addition, the ablation zone rapidly involutes over time.

Histotripsy uses high-amplitude, low-duty–cycle ultrasound pulses to create cavitation at the focal zone. This technique is distinct from thermal HIFU, which uses a longer application of ultrasound energy to create focal heating (20). In contrast, the high peak negative pressures from histotripsy mechanically destroy tissue without heating.

The ablation zones created in our study were precise, with a narrow zone of partial necrosis between ablated and unablated tissue and no peripheral hypoperemia. The precision of RAST would be important when treating tumors near vulnerable structures such as bile ducts or bowel. In our study, no evidence of collateral damage in the liver

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### Table 1

<table>
<thead>
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<th>Variable</th>
<th>Prescribed*</th>
<th>Actual†</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td>14</td>
<td>25.7 ± 10.8</td>
<td>.008</td>
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<tr>
<td>Anteroposterior (cm)</td>
<td>3.0</td>
<td>3.4 ± 0.65</td>
<td>.083</td>
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<tr>
<td>Transverse (cm)</td>
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<td>3.2 ± 0.68</td>
<td>.292</td>
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<tr>
<td>Craniocaudal (cm)</td>
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<td>3.8 ± 1.07</td>
<td>.043</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>1</td>
<td>0.986 ± 0.0099</td>
<td>&lt;.001</td>
</tr>
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</table>

Note.—RAST = robotically assisted sonic therapy.
* Numbers are raw data.
† Data are means ± standard deviation.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate (n = 10)</th>
<th>Follow-up (n = 6)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Ablation diameter (cm)</td>
<td>3.5 ± 0.8</td>
<td>2.4 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ablation volume (mL)</td>
<td>25.7 ± 10.8</td>
<td>11 ± 6.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note.—Data are means ± standard deviation. RAST = robotically assisted sonic therapy.
or nearby organs was found despite closely placed ablation zones. In fact, some ablations contained patent bile ducts excreting gadoxetate disodium at delayed postcontrast imaging.

Evaluation of the RAST ablation zones from acute subjects demonstrated ablation zones corresponding well to the software-prescribed size and shape with a narrow zone of partial necrosis at the periphery. The largest discrepancy between the planned and actual size was in the craniocaudal dimension, where the mean diameter was 3.8 cm compared with the planned 3.0 cm. This discrepancy was likely because of the fact that the liver moved up and down with free breathing throughout the ablation. The histopathologic finding of a variable zone of partial necrosis also likely relates to this respiratory motion, causing liver parenchyma on the boundary of the ablation zone to move in and out of the therapy pulse. Our hypothesis is supported by previous studies showing sharply demarcated ablation zones, including bisected cells at the lesion boundaries in cases with minimal breathing motion (10,18).

Evaluation of the RAST ablation zones in chronic subjects demonstrated a fibrous capsule separating the ablation zone from the adjacent untreated liver. Acute venous thrombosis near the ablation zone either improved or resolved at 4-week follow-up imaging.
This finding is similar to results with thermal ablation modalities (21,22), and the short-term resolution and lack of associated symptoms suggest a clinically insignificant finding.

RAST was able to rapidly create precise ablations without the need for incisions, punctures, or precise applicator placement. In addition, the coaxial mounting of a diagnostic transducer with the therapy transducer allows accurate targeting with planning before ablation and real-time monitoring of the ablation. For this feasibility study, a 3-cm sphere was selected as the largest ablation zone that could be reliably created. However, in the future, virtually any size and shape of ablation zone could be software prescribed.

The occurrence of body wall injury in a few cases was largely a result of user inexperience, a nonoptimized prototype pulse sequence, and a poor sonographic treatment window. In the porcine model, the tightly spaced ribs and air-distended stomach limit the sonographic window to the liver. When the treatment location was appropriately selected with an unobstructed sonographic window and visualization of the echogenic bubble cloud, no off-target treatments or injuries occurred. Poor visualization of the bubble cloud should thus be considered a contraindication to proceeding.

Our study had several limitations. The treatment pulse sequence was not optimized for minimizing thermal dose or time in this proof-of-concept study, but optimization is currently underway in an additional set of experiments. Another limitation was the porcine model, which varies from humans in a way that limits what can be targeted. Histotripsy has previously been shown capable of destroying tumors without increasing metastatic spread (23,24), but further evaluation of RAST in a wider array of tumor models will be an important future direction. Although we evaluated the evolution of the ablation zone over a 4-week period, a longer follow-up time would provide a more complete characterization.

In conclusion, RAST was able to create clinically relevant porcine hepatic ablation zones in a short treatment period without inducing any substantial acute or chronic complications. Unlike currently available ablation modalities, RAST is both noninvasive and nonthermal, making it promising for potential future clinical use.

Disclosures of Conflicts of Interest: A.R.S. disclosed no relevant relationships. M.M.C. disclosed no relevant relationships. E.V. Activities related to the present article: is a former employee of HistoSonics and the University of Michigan. Activities not related to the present article: is a consultant for HistoSonics. Other relationships: disclosed no relevant relationships. A.G.F. disclosed no relevant relationships. G.G. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a shareholder in NeuWave Medical. Other relationships: disclosed no relevant relationships. J.C. Activities related to the present article: is an employee and equity holder of HistoSonics. Activities not related to the present article: disclosed no relevant relationships. Other relationships: has a patent pending. T.J.Z. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: receives personal fees from NeuWave Medical. Other relationships: disclosed no relevant relationships. F.T.L. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed no relevant relationships. E.V. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed no relevant relationships. T.J.Z. Activities related to the present article: is a board member of and holds stock in HistoSonics; is a consultant for Ethicon; institution receives grants from HistoSonics and money from Medtronic/Covidien for patents and royalties; author receives royalties from Medtronic/Covidien. Other relationships: disclosed no relevant relationships.

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