Noninvasive Creation of an Atrial Septal Defect by Histotripsy in a Canine Model

Zhen Xu, PhD; Gabe Owens, MD, PhD; David Gordon, MD; Charles Cain, PhD; Achi Ludomirsky, MD

Background—The primary objective of this study was to develop an image-guided, noninvasive procedure to create or enlarge an atrial septal defect for the treatment of neonates with hypoplastic left heart syndrome and an intact or restrictive atrial septum. Histotripsy is an innovative ultrasonic technique that produces nonthermal, mechanical tissue fractionation through the use of high-intensity ultrasound pulses. This article reports the pilot in vivo study to create an atrial septal defect through the use of extracardiac application of histotripsy in an open-chest canine model.

Methods and Results—In 10 canines, the atrial septum was exposed to histotripsy by an ultrasound transducer positioned outside the heart. Ultrasound pulses of 6-microsecond duration at a peak negative pressure of 15 MPa and a pulse repetition frequency of 3.3 kHz were generated by a 1-MHz focused transducer. The procedure was guided and monitored by real-time ultrasound imaging. In 9 of 10 canines, an atrial septal defect was produced, and shunting across the atrial septum was visualized. Pathology of the hearts showed atrial septal defects with minimal damage to surrounding tissue. No damage was found on the epicardial surface of the heart or other structures.

Conclusions—Under real-time ultrasound guidance, atrial septal defects were successfully created with extracardiac histotripsy in a live canine model. Although further studies in an intact animal model are needed, these results provide promise of histotripsy becoming a valuable clinical tool. (Circulation. 2010;121:742-749.)

Key Words: heart defects • congenital • septal defects • surgery • ultrasonics
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index of 12.25 This compares to the maximum mechanical index of 1.9. The peak negative pressure reaching the atrial septum was estimated to be 12 MPa, resulting in a mechanical index of 2.4. The attenuation caused by the excised porcine atrial tissue.22 This article reports a pilot study to create an ASD by histotripsy in a live beating heart using an open-chest canine model.

Methods

Canine Surgery

The procedures described here were reviewed and approved by the University Committee on Use and Care of Animals at the University of Michigan. A total of 10 healthy adult 25- to 40-kg mongrel dogs underwent the surgery. The animals were preanesthetized with acepromazine (3 mg IM), and anesthesia was induced with thiopental (8 to 12 mg/kg IV) after intravenous catheter placement. The dogs were intubated and placed on a surgical table. The animals were maintained on isoflurane (1% to 3%) inhalation anesthesia for the duration of the procedure. Each animal was monitored by a pulse oximeter. A sternotomy incision provided direct access to the heart.

Histotripsy Apparatus

Ultrasound pulses for histotripsy treatment were generated by an external high-power ultrasound therapy transducer. The transducer was submerged in a heated, degassed external water bag, which was coupled to the pericardium with a thin plastic membrane and ultrasound coupling gel. To place the ultrasound focus on the atrial septum, the therapy transducer was moved in the water bag to adjust its standoff distance to the pericardium.

The therapy transducer was designed in our laboratory and fabricated by Imasonic, SA (Besançon, France). The circular transducer has a center frequency of 1 MHz, a geometric focal length of 90 mm, an outer diameter of 100 mm, and a 40-mm inner hole for housing an ultrasound imaging probe (Figure 1a). The transducer was driven by a high-voltage amplifier built in-house. Ultrasound pressure waveforms of the therapy transducer were measured in degassed water with a fiberoptic probe hydrophone.23 The peak negative and positive pressures used in the following experiment were 15 and 61 MPa, respectively (Figure 1b). Taking into account the attenuation caused by the ~1-cm-thick atrial wall tissue in the pathway,24 the peak negative pressure reaching the atrial septum was estimated to be 12 MPa, resulting in a mechanical index of 12.25 This compares to the maximum mechanical index of 1.9 used in diagnostic ultrasound.25 The ultrasound waves were 6 micro-seconds in duration (6 cycles at 1 MHz) and separated by 300 microseconds (ie, pulse repetition frequency, 3.3 kHz). These acoustic parameters have been used successfully to create perforations in the atrial wall tissue in vitro.22

Pressures heating by separating short, intense pulses with long cool-down time (at least 20 times longer than the pulse duration). The treatment is guided and monitored in real time by standard ultrasound imaging.24 Previously, histotripsy was demonstrated to create clearly demarcated perforations in excised porcine atrial tissue.22 This article reports a pilot study to create an ASD by histotripsy in a live beating heart using an open-chest canine model.

Histotripsy Treatment

The entire histotripsy procedure was guided by ultrasound imaging. The targeting and monitoring of the procedure were achieved by a 5-MHz phased-array ultrasound imaging probe (GE VingMed System FiVe, GE, Waukesha, WIs) inserted into the central hole of the therapy transducer. Another 10-MHz phased-array imaging probe was used to achieve higher-quality imaging of the atrial septum before and after the procedure by placing it directly on the epicardial surface of the heart.

The first step in the histotripsy procedure was to target the therapy focus to the atrial septum. Before the procedure, histotripsy pulses were applied to a waterbath, resulting in a bubble cloud and a bright (hyperechoic) zone on a 2-dimensional ultrasound image. The front center of the hyperechoic zone was marked as the focal position (Figure 2). Although the hyperechoic bubble zone generated in the water could be 7 to 8 mm wide, the bubble zone created in the blood on the tissue was 2 to 4 mm. The therapeutic transducer was then moved by a 3-axis positioning system (Parker Hannifin, Rohnert Park, Calif) to align the focus marker on the atrial septum surface in the right atrium. To verify the targeting accuracy, a small number of pulses were applied to produce a hyperechoic zone on the atrial septum.

Once the targeting was accomplished, histotripsy ultrasound exposures of 2 minutes were applied to the atrial septum at 1 time. After every 2 minutes of exposure, the atrial septum was scanned by 2-dimensional imaging and Doppler color-flow mapping to identify whether blood flow was seen across the atrial septum. Repetitive 2-minute exposures were delivered to the atrial septum until an ASD was generated.

Posttreatment Process

Within 1 hour after the ASD creation, animals were euthanized with a lethal dose of pentobarbital (100 mg/kg IV). The heart was extracted, fixed in a 10% formalin solution, and dissected after 1 week of fixation. The atrial septum and the rest of the heart were first examined by gross evaluation and then processed with standard hematoxylin and eosin (H&E) staining for pathological evaluation.

Collection of Human HLHS Patient Data

To evaluate the relevance of the canine study to the applicability of histotripsy to human, important geometric and anatomic data on human HLHS neonatal patients were collected. Available acoustic window position and size; the thickness, size, and motion of the atrial

Figure 1. a. The 1-MHz histotripsy therapy transducer with an ultrasound imaging probe inserted in its central hole. b, Ultrasound pressure waveform of the histotripsy pulse at the transducer focus measured by a fiberoptic hydrophone.

Figure 2. Before the treatment, a bubble cloud was generated in a waterbath, which was shown as a hyperechoic zone on an ultrasound image and used for target localization. Ultrasound was delivered from the top to the bottom. The front center of the hyperechoic zone was marked as the focal zone (x). The image was collected with a 5-MHz imaging probe inserted in the central hole of the therapeutic transducer.
septum; the thickness of overlying tissues in the ultrasound beam path; and the distance between these tissues were measured by analyzing patient echocardiography data. A total of 47 neonatal HLHS patients with an intact or restrictive (defined by a left-atrial-to-right-atrial pressure gradient of $\geq 5$ mm Hg and/or reversal of flow in the pulmonary veins) atrial septum who received ultrasound imaging at Washington University Children’s Hospital during the past 10 years were included. These neonatal patients weighed 2.5 to 3.9 kg (mean, 3.4 kg) and were 1 to 3 days of age. All of the patients underwent a complete 2-dimensional and Doppler study with the commercially available ultrasound imaging system (Philips Sonos 5500, Siemens Sequoia and GE Vivid 7). The above procedures were fully approved by the institutional review board at Washington University Medical School and the University of Michigan.

### Results

In 9 of the 10 in vivo canine heart experiments, an ASD was successfully generated in 6 to 16 minutes of histotripsy treatment (Table 1). The ASD generation was verified with ultrasound imaging, color-flow Doppler mapping, gross morphology, and pathological evaluation. All of the animals survived the immediate procedure, and there were no complications such as pericardial effusions or sustained arrhythmias.

#### Ultrasound Imaging

During the procedure, generally a $\approx 2$- to 4-mm-wide bubble cloud was created at the focus on the atrial septum. The histotripsy ultrasound pulses went through the right atrium to reach the atrial septum. When the procedure was progressing normally, the bubble cloud appeared as a temporally changing (twinkling) hyperechoic zone on the ultrasound image (Figure 3a). The ultrasound image was disturbed by a small number of lines caused by the interference from the short histotripsy ultrasound pulses, but the image quality was sufficient for real-time monitoring.

The atrial septum was constantly moving during the histotripsy procedure because of the heart contraction and respiration motion. The ultrasound image showed that the atrial septum motion was mostly along the axial direction of the therapy ultrasound beam and perpendicular to the atrial septum, measured to be 8.1 $\pm$ 3.3 mm (mean $\pm$ SD; Table 1).

The atrial septum also had motion in and out of the ultrasound image plane in the lateral direction of the ultrasound beam.

### Table 1. Summary of Results

<table>
<thead>
<tr>
<th>Canine</th>
<th>Treatment Time, min</th>
<th>Atrial Septal Axial Motion, mm</th>
<th>Ultrasound (Center),* mm</th>
<th>ASD, mm Pathology†</th>
<th>Hemorrhage, mm Pathology‡</th>
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<tr>
<td>1</td>
<td>6</td>
<td>5.2</td>
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<td>8.1</td>
<td>3.4</td>
<td>5.0</td>
<td>2.6</td>
</tr>
</tbody>
</table>

RA indicates right atrial; LA, left atrial.

*Width of the color jet in the center of the ASD measured on ultrasound Doppler images.
†Widths of the acellular zone in the ASD for the right and left atrial surfaces measured from pathology analysis with H&E cross-section slides.
‡Widths of the eosinophilic and hemorrhagic rim surrounding the acellular ASD zone for the right and left atrial surfaces. This width is measured from the outermost edge of the acellular zone to the outermost edge of eosinophilic myocyte and hemorrhage zone on either side of the ASD. For each ASD, this measurement was performed for both sides of the ASD and using multiple slides across the same ASD, and the maximal value of the measurements is reported.
§Pathological evaluation on the heart of dog 9 could not be obtained because it was filled with heartworms; however, ultrasound Doppler confirmed the ASD creation.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** a, During the treatment, a bubble cloud was generated on the atrial septum by histotripsy, which showed as a temporally changing, hyperechoic (bright twinkling) zone on the ultrasound image (arrow). The ultrasound image has a few disturbed B-scan lines as a result of the interference from histotripsy pulses. b, Before the ASD creation, erosion of the atrial septum generated by histotripsy appeared as a dark groove in the atrial septum (arrow). The images were collected with a 5-MHz imaging probe. RA and LA indicate right atrium and left atrium, respectively.
Unfortunately, the extent of lateral motion could not be evaluated precisely with this setup.

As the treatment progressed, the bubble cloud eroded the atrial septum layer by layer within the treatment zone. Before the completion of the ASD, the erosion appeared as a dark indentation in the atrial septum on the ultrasound image, with the opening facing the right atrium, which was the ultrasound entrance side (Figure 3b). When the atrial septum was perforated, the ASD could be seen as a dark channel through the atrial septum by 2-dimensional ultrasound imaging (Figure 4). The ASD creation was further confirmed by color-flow Doppler mapping revealing left-to-right shunting across the atrial septum (Figure 4). The width of the color jet through the ASD was measured on Doppler images (3.40 ± 0.9 mm) and is listed in Table 1.

**Gross Morphology**

Hemorrhage indicated by dark colorization was observed on both sides of the treated atrial septa where an ASD was created. The location of the ASD was consistent with that indicated on ultrasound image. The diameter of the dark-colored area (including the ASD) was larger on the right atrial side (∼4 to 10 mm in diameter; Figure 5a) and smaller on the left atrial side (∼2 to 5 mm in diameter; Figure 5b). The cross-section of the atrial septa showed cone-shaped lesions extending all the way through the atrial septum, with a larger opening on the right atrial side compared with the left. These results are consistent with the fact that the histotripsy ultrasound pulses reached the atrial septum from the right atrium.

The whole hearts appeared intact from the outside, with no visible damage on the epicardial surfaces (Figure 5c and 5d). After dissection, in 9 of 10 cases, no gross damage was observed inside the heart other than in the treatment area in the atrial septum (Figure 5e). In only 1 of the 9 successful cases, small areas of discoloration were found on the anterior wall of the right atrium (Figure 5f), which was in the pathway of the histotripsy ultrasound pulses, just opposite the created ASD.

**Pathology**

On the H&E-stained slides, the central damage zone of the ASD contained acellular tissue debris and red blood cells (Figure 6a and 6b). Other than the red blood cells, no discernible intact cellular structures remained. It appeared that variable degrees of thrombus formed within the ASD (Figure 6b). Because all of the ASDs were patent with blood flow up to the time of euthanasia confirmed by Doppler, the thrombus is likely postmortem; however, the possibility of premortem thrombus formation partially obstructing the defect cannot be excluded. This necrotic zone extended from the right atrial surface all the way to the left, suggesting complete penetration through the atrial septum and creation of an ASD. The cross-section of the acellular zone was generally cone shaped. The width of the acellular zone measured on H&E cross-section slides was 5.0 ± 1.1 mm on the right atrial surface and 2.6 ± 0.4 mm on the left (Table 1).

Immediately outside the acellular zone was a rim of hemorrhage and structurally intact myocytes with a more eosinophilic hue compared with the normal myocytes, suggesting early contraction necrosis (Figure 6c). These myocytes were likely affected by histotripsy. Beyond this rim of damaged cells were normal-appearing myocytes with no further discernible damage (Figure 6d). The width of the eosinophilic and hemorrhagic rim surrounding the acellular ASD zone was measured from the...
outermost edge of the acellular zone to the outermost edge of
the eosinophilic myocyte and hemorrhage zone on either side of
the ASD. For each ASD, this measurement was performed for
both sides of the ASD for the right and left atrial surfaces and
using multiple slides across the same ASD, and the maximal
value of the measurements is reported as the hemorrhage width in
Table 1.

Histology of the atrial wall tissues in the ultrasound
pathway appeared normal. In the 1 case in which the anterior
wall of the right atrial wall had slight discoloration on
morphology, H&E slides showed intact and normal-
appearing myocytes with slight hemorrhage (Figure 7).

The Failure Case
In the 1 treatment in which an ASD was not generated,
ultrasound went through first the right ventricle and then the
right atrium to reach the atrial septum. This pathway is
different from our other treatments in which ultrasound
reaches the atrial septum through the right atrium directly.
With the pathway used in the failure case, the atrial septum has a significantly larger motion with respect to the ultra-
sound beam (17.1-mm axial motion). In this case, the atrial
septum was eroded but not perforated. This treatment was
also performed early in the series of experiments, when the
treatment procedures were not well developed.

Collection of Human HLHS Patient Data
The measurements based on echocardiography of 47 human
HLHS neonatal patients with an intact or restrictive atrial
septum showed a subcostal acoustic window with a length of
5.1 to 6.7 cm. From the subcostal window, ultrasound can
access the atrial septum without bone or lung obstruction. To
reach the atrial septum, the ultrasound beam would go
through the abdominal skin, the right atrial wall, and some-
times a small portion of the liver. The ultrasound beam could
be positioned perpendicular to the atrial septum. Measure-
ments of the thickness and size of the atrial septum, the
motion of the atrial septum, the thickness of overlying tissues
in the ultrasound beam pathway, and the distance between
these tissues are reported in Table 2.

Discussion
This study has demonstrated the feasibility of creating an ASD
through epicardial application of histotripsy. The treatment
targeting and monitoring are guided in real time by ultrasound
imaging. The ASD creation is precise and reproducible.

Ultrasound Imaging Guidance
The treatment targeting is guided by a temporally changing,
hyperechoic bubble cloud zone on ultrasound image. The location of the bubble cloud indicates the focal position and
is used to target the focus to a preselected tissue volume such

Figure 6. Representative H&E-stained slides of the canine ASD lesion gener-
a by histotripsy. a. Full view of an
ASD lesion. The ASD region containing
necrotic acellular debris is approximately
outlined by the dashed lines. The right
atrium is on the top side of the atrial
septum, and the left atrium is at the bot-
tom. b, c and d, Magnified (×90) views
of the atrial septum corresponding to the
areas indicated in a. b, Center of ASD
showing complete fractionation of cellu-
lar structures, plus some trapped red
blood cells with platelets and fibrin.
c, A few hundred microns away from the
acellular debris, hemorrhage and struc-
turally intact myocytes with a more
eosinophilic hue are seen. d, Completely
normal-appearing myocytes beyond the
eosinophilic myocytes.

Figure 7. H&E-stained slides of the right atrial wall
that was slightly damaged by the treatment at ×4
(a) and ×20 (b) magnifications. b. An expanded
view of the area outlined by rectangular lines in a.
The ASD generated by histotripsy in this study has a diameter of 2.6±0.4 mm on the left atrial surface and 5.0±1.1 mm on the right atrial surface, with an ≈1- to 4-mm rim of injury surrounding the ASD. We did not observe any clear trend for the dependence of the ASD diameter and the width of surrounding injury on the treatment time or motion of the atrial septum; however, only 1 acoustic parameter set was used here. Our previous in vitro experiments have shown that acoustic parameters can significantly affect the diameter and boundary condition of ASD.22,26 For example, shorter pulse duration and lower-duty cycle produce smaller ASD and smoother boundary. Further studies are planned to explore the acoustic parameter sets that can minimize the surrounding injury. In this study, the injury to the surrounding tissue may be underestimated because a 1-hour waiting time between treatment completion and euthanasia of the animal may not be sufficient for all potential inflammatory effects and myocardial injury to become recognizable by light microscopy. We also plan to perform short-term and long-term studies to evaluate whether this injury is reversible.

Although no clear trend was observed on the effect of septal motion on the surrounding injury, the septal motion probably contributes to generating the collateral damage by exposing surrounding septal tissue to the histotripsy ultrasound beam. In the canine model, the movement of atrial septum along the axial ultrasound beam is 8.1±3.3 mm. There is also movement along the lateral beam estimated up to 4 to 5 mm. In comparison, the axial and lateral movement of human HLHS patients is measured to be ≈1 to 2 mm. With less movement of the atrial septum in human neonates, it is expected that less collateral damage would be produced. At the same time, the critical structures in the neonatal heart are in closer proximity, and higher accuracy will be required.

To reduce the effect of septal motion and to further increase treatment accuracy, there are 2 possible solutions. First, one could synchronize the histotripsy treatment pulses with the patient’s heartbeat and respiration, with the pulses applied only when the atrial septum moves to the same location. This synchronization approach is straightforward to achieve and has been used for HIFU epicardiac ablation,15,17 but the treatment is prolonged because time is wasted when the atrial septum moves out of that location. The second approach uses motion tracking to maximize the treatment accuracy while minimizing the treatment time. The therapy focal position is steered electronically to track the atrial septum movement in real time27 and is technically challenging. We have designed and constructed phased-array therapeutic transducers that can electronically steer the transducer focus instantaneously. Other researchers have demonstrated that the movement of the atrial septum can be obtained from ultrasound imaging.28

As a result, the imaging quality during the treatment is less than desired. To use a higher-frequency imaging probe and improve the imaging quality, a therapy transducer with a shorter focal length is needed and is being developed.

### Technical Challenges

In the canine experiments studied here, open-chest surgery was performed, and the transducer was positioned outside the

### Embolization Risk

Because histotripsy mechanically erodes the atrial septum, there is concern that the eroded tissue debris may become hazardous emboli, especially in single-ventricle physiology. We measured the size distribution of the tissue debris particles in a separate in vitro study.19 Measurements showed no particles >60 μm in diameter, and >80% of the particles were <6 μm. Such particles are unlikely to form hazardous emboli because 100-μm mechanical filters have been successful at preventing embolization in catheter-based thrombolysis procedures.29 There may, however, be a high risk for portions of newly developing mural thrombi at the site of tissue injury or necrotic tissue surrounding the ASD to embolize over time. To investigate the risk of embolization during treatment and over time, we plan to use transcranial Doppler during treatments and to perform postprocedure diffusion-weighted magnetic resonance imaging and pathology of the brain, lungs, and kidneys in our future short-term and long-term studies.

### Table 2. Echocardiographic Measurements From 47 Human HLHS Neonates With an Intact or Restrictive Atrial Septum*

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Coronal View, mm</th>
<th>Sagittal View, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin to RA wall</td>
<td>21.5–28.0</td>
<td>20.7–27.5</td>
</tr>
<tr>
<td>RA wall to atrial septum</td>
<td>11.2–18.5</td>
<td>11.4–17.5</td>
</tr>
<tr>
<td>Atrial septum length</td>
<td>11.2–17.4</td>
<td>11.5–17.2</td>
</tr>
<tr>
<td>Atrial septum thickness</td>
<td>1.7–2.2</td>
<td>1.5–2.1</td>
</tr>
<tr>
<td>Septum to LA wall</td>
<td>7.7–10.4</td>
<td>8.8–11.4</td>
</tr>
<tr>
<td>Septal motion</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>RA free wall motion</td>
<td>1–3</td>
<td>1–3</td>
</tr>
<tr>
<td>LA free wall motion</td>
<td>0–1</td>
<td>0–1</td>
</tr>
</tbody>
</table>

RA indicates right atrial; LA, left atrial.

*Measurements were obtained with echocardiography from the subcostal coronal and sagittal views. The subcostal window was selected because a subcostal acoustic window exists in human neonates for the ultrasound beam to access the atrial septum without obstruction from lungs or bones.
heart. Ultimately, to treat neonatal patients noninvasively, the ASD will be created with an extracorporeal application. Because ultrasound does not penetrate dense bone or air found in lungs, an ideal acoustic window to access the atrial septum would have to avoid these structures. Echocardiography from neonatal patients shows that such an acoustic window exists subcostally. The atrial septal length in infants with HLHS ranges from 11.2 to 17.4 mm (Table 2). This approach, however, requires a smaller therapy transducer with a shorter focal distance than the current transducer. The shorter standoff distance would allow a higher-frequency imaging probe and would provide better imaging quality for treatment targeting and monitoring. We are in the process of developing a 6×4-cm therapy transducer with a 5-cm focal distance. This therapy transducer will house an 8- to 12-MHz imaging probe and should be suitable for human neonatal use.

In the open-chest model, ultrasound has to penetrate only ~1 cm of the right atrial free wall. In the human neonatal patients, using the subcostal window, ultrasound needs to go through ~3- to 4-cm-deep tissue, including abdominal skin, liver, and the right atrial free wall, to reach the atrial septum (Table 2). Multiple layers of tissue with various acoustic properties would increase the ultrasound attenuation and aberration and affect the focal volume size and beam profile. Previous studies have shown that histotripsy can produce sufficiently high pressure through 3- to 4-cm overlying tissue and create accurate lesions in organs such as prostate. We have also started experiments in an intact neonatal pig model; early results show that histotripsy can produce accurate lesions through multiple layers of tissue, including neonatal ribs. We plan to continue our preclinical investigations and development of histotripsy in intact animal models.

Acknowledgments
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Disclosures
None.

References
CLINICAL PERSPECTIVE

Although previous studies have reported successful cardiac tissue ablation with high-intensity focused ultrasound using a mechanism of thermal necrosis, our study is the first to report targeted tissue fractionation and creation of an atrial septal defect in a beating heart using extracardiac ultrasound through controlled acoustic cavitation, or histotripsy. In an open-chest canine model, histotripsy generated demarcated tissue destruction through the targeted region of atrial septum with no insult to other cardiac structures and modest damage to adjacent septal tissue. Continued advances in probe design and motion-tracking algorithms should minimize this collateral damage. Although further studies are necessary to determine the efficacy and safety of this technology in an intact neonatal animal model, this initial report provides the first evidence that histotripsy may be a useful, minimally invasive clinical tool to create atrial septal defects or other intracardiac communications in infants with congenital heart diseases.
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