Canine Model of Esophageal Injury and Atrial-Esophageal Fistula After Applications of Forward-Firing High-Intensity Focused Ultrasound and Side-Firing Unfocused Ultrasound in the Left Atrium and Inside the Pulmonary Vein

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**Background**—Left atrial–esophageal fistula is a serious and poorly understood complication of catheter ablation of atrial fibrillation. The purpose of this study was to (1) develop a canine model of esophageal injury and left atrial-esophageal fistula after applications of forward-firing high-intensity focused ultrasound (HIFU) and side-firing unfocused ultrasound (SFU); (2) examine the relationship to esophageal temperature (Eso-temp); and (3) study the evolution of injury/healing.

**Methods and Results**—Twenty dogs were studied. After transeptal puncture, HIFU catheter (ProRhythm Inc; 13 dogs) was positioned close to the esophagus, either outside (n = 6) or inside (n = 7) the inferior pulmonary vein (PV). In 7 other dogs, an SFU catheter was placed deep inside the PV, close to the esophagus. A balloon (20- to 25-mm diameter) with 7 thermocouples (2-mm separation) was positioned in the esophagus (Eso-balloon). Variable air filling of the Eso-balloon controlled the distance from the esophagus to the sonication source, pressing the esophagus against left atrium/PV. One to 9 (median, 5) HIFU (35 W) and 5 to 7 (median, 5) SFU (40 W) sonications were delivered for 40 seconds. Maximum luminal Eso-temp was closely related to HIFU Eso-balloon distance. For HIFU outside PV, Eso-temp ≤ 50°C occurred only for HIFU Eso-balloon distance ≤ 2 mm. For HIFU/SFU inside the PV, Eso-temp was ≥ 50°C, with HIFU Eso-balloon distance up to 6.8 mm. Endoscopy identified esophageal ulcer immediately after ablation in 11 of 13 HIFU dogs and 7 of 7 SFU dogs, all with Eso-temp ≥ 50°C. Endoscopy at 2 weeks showed ulcer healing in 5 of 11 chronic dogs and ulcer size progression with relaxation of the lower esophageal sphincter and esophagitis in 6 dogs. Two dogs developed left atrial-esophageal fistula and died at 2 weeks.

**Conclusions**—This model produces esophageal ulcer when Eso-temp is ≤ 50°C. Eso-temp is higher with HIFU/SFU applications closer to the esophagus and with HIFU/SFU applications inside the PV. Ulcer progression and left atrial-esophageal fistula were associated with reflux esophagitis. *(Circ Arrhythmia Electrophysiol. 2009;2:41-49.)*

**Key Words:** catheter ablation ■ atrial ■ fibrillation ■ complications

Catheter ablation at the orifice or antrum of the pulmonary veins (PVs) is effective in eliminating atrial fibrillation (AF). However, a number of complications including arterial thrombo-embolism, PV stenosis, phrenic nerve injury, and pericardial tamponade have been reported. Esophageal injury manifested as esophageal perforation or left atrial (LA)-esophageal fistula has been reported after catheter or surgical ablation of AF using radiofrequency (RF) current and, more recently, following catheter ablation using high-intensity focused ultrasound (HIFU). This complication is associated with a very high morbidity and mortality, including air embolism, sepsis, and endocarditis. A LA-esophageal fistula usually presents 2 to 4 weeks after ablation. The factors leading to esophageal injury and the development of LA-esophageal fistula remain unclear. The purpose of this study was to develop a canine model of esophageal injury and LA-esophageal fistula using forward-firing HIFU and side-firing ultrasound (SFU) applications in the LA and inside the PV close to the esophagus. We also sought to determine the relationship between esophageal injury and peak esophageal...
temperature and examine the factors associated with esophageal ulcer progression using endoscopy and histology.

Methods
The experimental study protocol was approved by the University of Oklahoma Committee on the Use and Care of Animals. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written. Twenty adult mongrel dogs (29 to 38 kg) were studied. General anesthesia was administered with propofol (3 mg/kg per min) or pentobarbital (25 mg/kg), and the dog was ventilated mechanically. A 20-gauge catheter was inserted into the left femoral artery for monitoring arterial pressure. A 7F, 20-electrode catheter was inserted percutaneously into the right jugular vein and advanced under fluoroscopic guidance into the coronary sinus and great cardiac vein. A 10F ultrasound catheter (AcuNav Acuson, Inc) was inserted percutaneously into the left femoral vein and advanced into the right atrium to be used for intracardiac echocardiography. An 8F transseptal sheath was inserted percutaneously into the right femoral vein and advanced to the right atrium. Heparin (5000 U) was administered intravenously, with additional doses (2000 U), as necessary to maintain the ACT/H11022 300 seconds. Transeptal puncture was then performed under intracardiac echocardiography-guidance, placing the 8F sheath into the LA. The 8F transseptal sheath was exchanged for a 16.5F sheath.

Forward-Firing HIFU Balloon Catheter
In 13 of the 20 dogs, a deflectable, a HIFU balloon catheter (ProRhythm Inc, Ronkonkoma, NY)* was inserted through the 16.5F sheath into the LA and advanced to the left or right inferior PV, whichever was closest to the esophagus. The catheter has a central lumen for a guide wire (0.035 in) to guide the catheter to the PV. The central lumen was also used for occlusion PV angiography (distal to the balloon) to verify the location of the balloon and sonication ring, relative to the PV ostium. The HIFU balloon catheter has 2 attached noncompliant balloons (Figure 1A). The large-distal balloon (diameter, 24 mm) was filled with a mixture of water and contrast media (4:1 ratio) and contained the 9 MHz ultrasound crystal. The small proximal balloon was filled with carbon dioxide, forming a parabolic surface at the base of the distal (water and contrast) balloon to reflect the ultrasound energy in the forward direction. This focuses a 360°, 20-mm diameter ring (20-mm sonicating ring) 2 to 5 mm in front of the distal balloon surface (Figure 1A and 1B). Once inflated, the distal balloon was irrigated (water and contrast mixture in) at 20 mL/min (closed-loop) to cool the balloon and maintain balloon surface temperature ≤42°C during sonication. The pressure of the distal balloon was maintained at 8 PSI to hold the parabolic shape. The pressure of the proximal balloon was maintained at 1.2 PSI.

Side-Firing Unfocused Ultrasound Balloon Catheter
To maximize injury to the esophagus, a side-firing unfocused ultrasound (SFU) balloon catheter was custom made (ProRhythm with contrast and water at 20 mL/min during ablation to keep the balloon cool (≤42°C). B, Radiograph in the left anterior oblique projection showing the position of the HIFU balloon (20-mm sonicating ring, red arrows, and red-dotted line) and the esophageal balloon (Eso-balloon, 2.5-cm diameter) filled with air (yellow-dotted line). The HIFU balloon is located outside the left inferior PV. Seven thermocouples on the Eso-balloon are facing the LA. The distance between the sonication ring of the HIFU balloon and the Eso-balloon is 3 mm. HIFU application (acoustic power: 35 W, 40 seconds) at this site resulted in the maximum LET of 40°C. C, Radiograph in the LAO projection showing the SFU balloon (15-mm diameter) located inside the esophageal balloon (yellow-dotted line) is 3.1 mm. Ultrasound energy (40 W, 40 seconds, red arrows) was delivered inside the left inferior PV, resulting in the maximum LET of 95°C.
Eso-balloon was inserted into the esophagus, inflated to ablation and to place the esophagus close to the ablation site in the procedure after low and high esophageal temperature sonications to determine the relationship between esophageal temperature and injury. The diameter (long axis, L and short axis, S) of esophageal ulceration was measured by endoscopy or by gross examination. The area of ulceration was calculated using the following formula: π(LS/4).

Nine dogs were euthanized within 30 minutes following the final sonication for gross and histological examination of the esophagus and LA. These 9 “acute” dogs included the following: (1) all 6 dogs that received HIFU applications outside the PV (inside the LA); (2) 2 of the 7 dogs that received HIFU applications inside the PV; and (3) 1 of the 7 dogs with SFU applications deep inside the PV (Table 1). These 9 dogs also include the first 2 dogs, which did not undergo esophageal endoscopy.

The remaining 11 dogs were recovered from anesthesia (“chronic” dogs). Esophageal endoscopy was repeated (after fasting for 20 hours) at 1, 2, and 4 weeks following ablation. These dogs were euthanized at 4 weeks following ablation. Gross and histological examination of the esophagus and LA was performed. All 11 chronic dogs had sonication performed inside the PV (5 HIFU and 6 SFU; Table 1).

Statistical Analysis
Statistical analyses were done using SAS software (version 9, SAS Institute, Cary, NC). Values are expressed as mean±SD unless otherwise described. Distribution of the maximum LET among the 7 thermocouples on the Eso-balloon is described using side by side box plots. The significance of the relationship between maximum LET and the distance from the HIFU/SFU balloon to the Eso-balloon was assessed by repeated-measures ANOVA to account for the correla-
tion among the observations from individual dogs. One-factor repeated-measures ANOVA was used to assess the association between maximum LET and sonication site (inside and outside the PV). The relationship between maximum LET and size of esophageal ulcer was assessed using simple linear regression. \( P < 0.05 \) was considered to be statistically significant.

**Results**

**Distribution of LET**

The LET was measured by each of the 7 thermocouples (2 mm apart) on the Eso-balloon (Figure 2A). The temperature differed widely between the 7 thermocouples during sonications, which produced a maximum temperature of 50°C (Figure 2B and 2C). The maximum temperature was localized to a small area. The highest value recorded from the 7 thermocouples for each sonication was used as the maximum luminal LET.

**Relationship Between Maximum LET and Distance From Sonication (HIFU/SFU) Balloon**

During sonication, the maximum LET increased significantly with decreasing distance between the HIFU/SFU balloon and the Eso-balloon (Figure 2A). In the 6 dogs with HIFU applications in the LA outside the PV, the maximum LET ranged from 32°C to 66°C and was \( \geq 50°C \) only when the sonication ring on the HIFU balloon was located within 2 mm of the Eso-balloon (Figure 3A). However, for the 14 dogs with HIFU (7 dogs) or SFU (7 dogs) applications inside the PV, the maximum LET was higher (range 37°C to 105°C) and was \( \geq 50°C \) when the sonication ring was located as far as 6.8 mm from the Eso-balloon (Figure 3B).

**Relationship Between Esophageal Injury and Esophageal Temperature**

An acute esophageal ulcer was present immediately after ablation in 18 of the 20 dogs. The esophageal ulcer was identified by endoscopy in 16 of the 18 dogs and by gross examination in the other 2 dogs (Figures 3 through 5). Esophageal ulcers were located in the region facing the left atrium, at the site of greatest atrial pulsation. Esophageal ulceration occurred in 4 of the 6 dogs which received HIFU applications outside the PV, all 7 dogs that received HIFU applications inside the PV, and all 7 dogs that received SFU applications inside the PV (Figure 3D).

In all 18 dogs with acute esophageal ulceration, the maximum LET during sonication was \( \geq 50°C \) (Figure 3C). In the 2 dogs without an esophageal ulcer, the maximum LET was only 41°C. Endoscopy was performed 2 to 3 times during the ablation procedure in 10 dogs. Ulceration was absent after HIFU/SFU applications with a maximum LET of \( <42°C \) and consistently present after sonication producing a maximum LET of \( \geq 50°C \) (Figure 3C).

The size (area) of the esophageal ulcer increased significantly with increasing maximum LET (Figure 3D). A direct

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**Table. Ablation Parameters and Esophageal Temperature and Ulceration**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>No. of Applications</th>
<th>Min Distance, mm</th>
<th>Max Eso Temp, °C</th>
<th>Eso Ulcer, +/−</th>
<th>Immediately After</th>
<th>2 Weeks</th>
<th>4 Weeks</th>
<th>Esophagitis</th>
<th>LA-Eso Fistula</th>
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<td>*</td>
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<td></td>
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Min Distance indicates minimum distance between the HIFU/SFU balloon and the esophagus; Max Eso Temp, maximum esophageal temperature; Eso Ulcer, +/−, presence or absence of esophageal ulcer immediately after ablation; Eso Ulcer Area, area of esophageal ulcer; LA-Eso Fistula, left atrial-esophageal fistula.

*Dog was euthanized 30 min after the final ablation. Therefore, no follow-up data.
†The dog died due to left atrial-esophageal fistula at 10 or 14 days following the ablation.

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relationship between maximum LET (highest value for all sonications in each dog) and ulcer size was present for both sonication in the LA (outside the PV) and sonication inside the PV (Figure 3D).

Histological examination in the 9 acute dogs (euthanized within 30 minutes after ablation) showed transmural coagulation necrosis of the LA or PV myocardium in all 9 dogs. There was no endocardial disruption or crater formation within the LA or PV. Histological examination of the esophagus showed segmental transmural coagulation necrosis of the esophageal wall with ulcer in 7 dogs, nontransmural esophageal necrosis without ulceration in 1 dog and no esophageal necrosis in 1 dog. Endoscopy in the 2 dogs with either no esophageal necrosis or nontransmural necrosis showed no ulcer. Endoscopy was performed in 5 of the 7 dogs with histological transmural esophageal necrosis and ulceration. Endoscopy identified the esophageal ulcer in all 5 dogs.

Evolution of Esophageal Injury Over 4 Weeks Following Ablation

All 11 chronic dogs underwent sonication inside the PV (5 HIFU and 6 SFU) and all had an esophageal ulcer by endoscopy immediately after ablation. In 5 of the 11 dogs, repeat endoscopy showed regression of the esophageal ulcer at 1 to 2 weeks and complete healing of the ulcer at 4 weeks after ablation (Figure 4; Table 1). Gross and histological examination at 4 weeks showed the healed ulcer with regeneration of the epithelium and segmental fibrosis of the mucosal and muscular layers (Figure 6). The esophageal lesion involved the periesophageal vagus nerves in only 1 of the 5 dogs.
The other 6 chronic dogs (54%) had progression of the esophageal ulcer size by follow-up endoscopy or autopsy. Endoscopy was performed at 1 to 2 weeks in 5 of the 6 dogs (Figure 4). The increase in ulcer size was associated with esophagitis (pale appearance of the esophageal wall surrounding the ulcer, Figure 7A) and relaxation of the lower esophageal sphincter (determined by endoscopy) in all 6 dogs and food in the esophagus (despite fasting 20 hours) in 2 of the 6 dogs (Figure 7A). These findings suggest the presence of gastro-esophageal reflux. Endoscopy at 4 weeks showed decreasing ulcer size (healing) with reduction or resolution of esophagitis in 4 of the 6 dogs (Figures 4 and 7A). Gross examination of the esophagus at 4 weeks in these 4 dogs showed incomplete healing of the ulcer (Figure 7B). Histological examination revealed segmental transmural fibrosis of the esophageal wall with incomplete regeneration of the epithelium (residual ulcer, Figure 7C). The esophageal lesions involved the periesophageal vagus nerves (Figure 7D) in all 4 dogs. The remaining 2 dogs developed fever at 8 and 10 days and died at 11 and 14 days following the ablation. Postmortem examination revealed a marked increase in esophageal ulcer size (from $15 \times 15$ mm immediately after ablation to $42 \times 28$ mm and from $15 \times 13$ to $40 \times 25$ mm) and a fistula between the esophagus and left inferior PV-LA (Figures 4 and 8A). There was esophagitis extending between the ulcer and the stomach in both dogs (Figure 8B). Histological examination showed transmural esophageal necrosis and fistula. The esophageal lesion involved large branches of the periesophageal vagus nerves in both dogs (Figure 8B). Both dogs underwent SFU ablation inside the PV. The maximum LET (70°C and 95°C) and the initial ulcer size were moderately high (asterisks in Figure 3D). Five other dogs without development of a fistula had higher maximum LET and a larger initial esophageal ulcer (Figure 3D).

Discussion

This study represents the first in vivo model of esophageal injury and LA-esophageal fistula occurring after catheter ablation of AF. This model used HIFU and SFU delivered close to the esophagus, either in the LA (outside the PV) or inside the PV. The primary findings include the following: (1) the occurrence of transmural esophageal necrosis with ulceration whenever the maximum LET reached or exceeded 50°C; (2) endoscopy accurately identified the presence of an esophageal ulcer (transmural esophageal necrosis) within minutes after a sonication producing a maximum LET $\geq 50°C$; (3) nontransmural esophageal necrosis was not associated with ulceration on endoscopy or histology; (4) the size of esophageal ulcer was directly related to the maximum LET; (5) there was a steep gradient of LET surrounding the sonication zone, such that very high temperatures were recorded in only a small area; (6) high LET ($\geq 50°C$, associated with esophageal ulcer) occurred only when the ultrasound energy was applied within 2 mm of the esophagus when sonicating in the LA outside the PV, but occurred with ultrasound applied at a distance of up to 6.8 mm from the esophagus when sonicating inside the PV; (7) the progression of esophageal ulcer size and the development of LA-esophageal fistula were associated with esophagitis and relaxation of the lower esophageal sphincter, suggesting a role for gastro-esophageal reflux in the progression of esophageal injury; and (8) relaxation of the lower esophageal sphincter may result from injury to the periesophageal vagal plexus.

These findings may have clinical implications for catheter ablation of AF. Esophageal perforation and LA-esophageal fistula have occurred in 1 patient each at 2 weeks following HIFU ablation of AF. The present study suggests that, when sonicating in the LA (outside the PV), maintaining a distance of at least 3 to 4 mm between the sonication ring and the esophagus may prevent esophageal injury. The reason this relatively short distance appears safe is because of the high absorption of 9 MHz ultrasound energy by the atrial myocardium, reducing the amount of energy absorbed by the esophagus. When sonicating inside the PV, a greater distance from the esophagus ($\geq 7$ mm) may be required to avoid esophageal injury. The lower absorption of ultrasound energy...
by the blood and thin PV wall probably results in greater absorption (heat) by the esophagus.

Esophageal ulceration is produced frequently in this canine model (18 of the 20 dogs). In a recent report, approximately one third of patients who underwent endoscopy following RF ablation of AF were found to have an esophageal ulcer.\textsuperscript{10} In our experience, 28 of 73 (38\%) patients who underwent endoscopy 1 day after RF ablation of AF were found to have an esophageal ulcer.\textsuperscript{11} The ulcer occurred despite low RF power (15 to 25 W) and terminating the RF application for any small increase in esophageal temperature (\(\pm 0.2^\circ\text{C}\)), measured by a single thermocouple on a thin flexible esophageal probe.\textsuperscript{11} The present canine study may help to explain the high incidence of asymptomatic ulceration (transmural thermal injury) with a low temperature rise (\(\pm 0.2^\circ\text{C}\)). The small area of high LET was probably missed by the single thermocouple, despite efforts to maneuver the esophageal probe as close as possible to the ablation catheter using fluoroscopy.\textsuperscript{12,13} These observations suggest that, to be effective in preventing esophageal ulceration, it would be necessary to measure the true maximum LET. A thermocouple or thermistor would have to be positioned against the anterior esophageal wall, directly opposite the ablation site in the LA for each RF application. One approach would be to use place an esophageal balloon with multiple, closely spaced temperature sensors, similar to the Eso-balloon used in this study. The inflated balloon would position the temperature sensors appropriately, but would also push the esophageal wall against the LA. The shorter distance and increased contact force might increase the risk of esophageal injury. Some investigators are exploring the use of cooling the esophageal balloon to protect against thermal injury.\textsuperscript{14–16} Alternatively, noncontact temperature probes, which would not compress the esophagus against the LA, are under development.

Although esophageal ulcers (transmural esophageal necrosis) occur frequently in patients undergoing AF ablation,\textsuperscript{10,11} the catastrophic development of a LA-esophageal fistula is relatively infrequent and usually presents 2 to 4 weeks after ablation.\textsuperscript{4–6,7} The process by which an esophageal ulcer progresses to a LA-esophageal fistula is poorly understood. In the 11 chronic dogs in the present study, endoscopy at 2 weeks after ablation showed healing of ulceration in 5 dogs and progression of ulceration in other 6 dogs (including 2 dogs that died due to LA-esophageal fistula at 11 and 14 days after ablation). Ulcer progression was associated with esophagitis (Figures 4 and 7A). Reflux esophagitis can result from malfunction of the lower esophageal sphincter and gastric hypomotility,\textsuperscript{17,18} both of which could be due to damage to the periesophageal vagal plexus during ablation as demonstrated in this model (Figures 7D and 8B). Our observation of food in the esophagus and stomach after 20 hours of fasting indicates the presence of both gastric hypomotility and malfunction of the esophageal sphincter in these dogs (Figure 7A). Reflux of gastric secretions may amplify the area of erosion and initiate fistula formation by digestion of esophageal tissue and atrial myocardium. This process may explain the delay of 2 to 4 weeks in development of fistula observed in this model and in patients. Measures to prevent reflux-induced esophagitis such as proton pump inhibitors\textsuperscript{19} and cytoprotective agents (such as sucralfate\textsuperscript{20}) may be beneficial to prevent fistula formation after AF ablation.

This model of esophageal injury and fistula formation may be useful in accessing and decreasing the risk of esophageal

\begin{figure}
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\includegraphics[width=\textwidth]{figure7}
\caption{Progression of esophageal ulceration associated with esophagitis. A, Endoscopic images of the esophagus immediately, 2 weeks, and 4 weeks after HIFU ablation. A single HIFU application inside the PV resulted in LET increase up to 61°C and produced an ulcer (7×3 mm, black arrows in the left panel) in the anterior wall of the esophagus facing to the posterior left atrium. Repeat endoscopy at 2 weeks after ablation showing progression of ulceration (25×7 mm, black and white arrows in the middle panel). The pale esophageal wall surrounding the ulcer indicates esophagitis. There was relaxation of lower esophageal sphincter. Note that there is food in the esophagus after 20 hours of fasting, suggesting gastric reflux (middle panel). At 4 weeks after ablation, the ulcer size of ulceration decreased (14×6 mm). B–D, Gross (B) and histological examination (C, trichrome stain) of the ulcer at 4 weeks after ablation showing transmural fibrosis. The ablation lesion involved the small branches of the periesophageal vagus nerves (D).}
\end{figure}
injury during AF ablation using other ablation systems, such as RF, laser, and cryo-thermia.

Study Limitations

The principal limitation of this canine model is the requirement to use an inflated esophageal balloon to move the esophagus close to the LA to mimic the short distances between the esophagus and the posterior LA in patients undergoing AF ablation. The pressure in the EsO-ballon may increase the contact force between the sonication balloon in the LA (or PV) and esophagus, increasing LA and esophageal injury. However, the endoscopic findings after ablation are similar to those in patients undergoing AF ablation using RF energy. Another limitation is that we did not explore other possible mechanisms of ulcer progression, including esophageal ischemia and infection after ablation.

Acknowledgments

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Disclosures

Drs Nakagawa and Jackman are consultants for ProRhythm. Mr Jung, Mr Merino, and Mr Zou are employees of ProRhythm. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Esophageal perforation and left atrial-esophageal fistula are serious and poorly understood complications of catheter ablation of atrial fibrillation. We developed a canine model of esophageal injury and left atrial-esophageal fistula after applications of forward-firing high-intensity focused ultrasound (HIFU) and side-firing unfocused ultrasound (SFU). Esophageal ulceration occurred only when the luminal esophageal temperature was ≥50°C, suggesting that luminal esophageal temperature monitoring during ablation may prevent esophageal injury. However, the present study showed that the highest luminal esophageal temperature was recorded in only a very small area, which is likely to be missed by the single thermocouple on currently available clinical esophageal temperature probes. Avoiding ablation within the pulmonary vein may reduce the risk of esophageal injury. HIFU energy delivered within the left atrium (outside the pulmonary vein) produced esophageal ulceration only when the distance between the HIFU balloon and the esophagus was ≈2 mm. The reason these relatively short distances (≥2 mm) appear safe is the high absorption of 9-MHz ultrasound energy by the atrial myocardium, reducing the amount of energy absorbed by the esophagus. In contrast, esophageal ulceration occurred with HIFU/SFU energy delivered inside the pulmonary vein at distances as long as 6.8 mm. In this canine model, progression of esophageal ulcer size and the development of left atrial-esophageal fistulae were associated with reflux esophagitis and relaxation of the gastro-esophageal sphincter. These findings might result from damage to the periesophageal vagal plexus during ablation. These observations support the use of a proton pump inhibitor following ablation to facilitate ulcer healing.
Canine Model of Esophageal Injury and Atrial-Esophageal Fistula After Applications of Forward-Firing High-Intensity Focused Ultrasound and Side-Firing Unfocused Ultrasound in the Left Atrium and Inside the Pulmonary Vein
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