Epicardial Catheter Ablation Using High-Intensity Ultrasound:
Validation in a Swine Model

Running title: Nazer et al.; Epicardial High-intensity Ultrasound Ablation

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Abstract:

**Background** - Epicardial radiofrequency (RF) catheter ablation of ventricular tachycardia (VT) remains challenging due to the presence of deep myocardial scar and adjacent cardiac structures such as the coronary arteries, phrenic nerve and epicardial fat that limit delivery of RF energy. High-intensity ultrasound (HIU) is an acoustic energy source able to deliver deep lesions through fat, while sparing superficial structures. We developed and tested an epicardial HIU ablation catheter in a closed-chest, in-vivo swine model.

**Methods and Results** - The HIU catheter is an internally-cooled, 14 French, side-facing catheter, integrated with A-mode ultrasound guidance. Swine underwent percutaneous sub-xiphoid epicardial access and ablation with HIU (n = 10 swine) at 15, 20 and 30 W. Compared to irrigated RF lesions in control swine (n = 5), HIU demonstrated increased lesion depth (HIU 11.6 ± 3.2 mm vs RF 4.7 ± 1.6 mm; mean ± SD) and epicardial sparing (HIU 2.9 ± 2.1 mm vs RF 0.1 ± 0.2 mm) at all HIU powers, and increased lesion volume at HIU 20 W and 30 W (p < 0.0001 for all comparisons). HIU ablation over coronary arteries and surrounding epicardial fat resulted in deep lesions with normal angiographic flow. Histologic disruption of coronary adventitia, but not media or intima, was noted in 44% of lesions.

**Conclusions** - Compared with RF, HIU ablation in-vivo demonstrates significantly deeper and larger lesions with greater epicardial sparing in a dose-dependent manner. Further development of this catheter may lead to a promising alternative to epicardial RF ablation.

**Key words**: ablation; ultrasound; ventricular tachycardia; epicardial
Introduction

Radiofrequency (RF) catheter ablation is recommended for patients with sustained ventricular tachycardia (VT) or recurrent implanted cardioverter defibrillator (ICD) shocks despite medical therapy\(^1\). However, when compared to patients with post-infarction VT undergoing ablation, patients with non-ischemic cardiomyopathy (NICMP) have higher VT recurrence rates, ranging from 47-67\% in long-term follow-up\(^2\)-\(^4\). This is largely because scar in NICMP patients is more often located in the mid-myocardium or epicardium\(^5\)-\(^6\), and the VT circuit is therefore difficult to reach given the limited depth of standard RF ablation (1.9 – 6.7 mm\(^7\)-\(^9\)).

Percutaneous subxyphoid pericardial access, pioneered by Sosa and colleagues\(^1\)\(^0\), has provided another route for mapping and ablating epicardial substrate in NICMP VT patients. However, many challenges remain. The presence of thick epicardial fibrotic tissue and overlying epicardial fat can limit the depth of RF ablation\(^9\), and RF ablation must be avoided near critical structures such as the coronary arteries or phrenic nerve\(^1\)\(^1\)-\(^1\)\(^2\). Additionally, mid-myocardial VT isthmuses may not be effectively treated by RF ablation from either endocardial or epicardial approaches, as VT associated with mid-septal scar (present in 12-45\% of NICMP VT patients) is effectively “shielded” from RF energy.

High-intensity ultrasound (HIU) is an energy source that applies ultrasound waves with a dedicated frequency (usually 1-10 MHz) at high amplitude (\(\sim\)10 megaPascals) to generate localized tissue heating and thermal necrosis\(^1\)\(^3\). HIU allows delivery of deep lesions with minimal effect on superficial tissue and structures, thus providing an attractive energy source for catheter ablation of NICMP VT.

We sought to develop a HIU catheter for epicardial VT ablation, and compare lesion characteristics with RF in swine, in-vivo. We hypothesized that HIU would lead to greater lesion
depth, volume, and epicardial tissue sparing compared with RF. We also sought to explore the safety of HIU ablation over epicardial coronary arteries.

Methods

Epicardial HIU Catheter Design

The HIU components were assembled on 14 French (Fr) flexible nylon catheter (Freelin-Wade Inc.; McMinnville, OR) (Figure 1). Separate lumens within the catheter house power feed lines and irrigation tubing. In order to assure orientation of the ablation beam toward the myocardium, an A-mode imaging crystal was added to the catheter. A-mode is the simplest type of ultrasound, whereby a single transducer scans a line through the heart with the echoes plotted on as a function of depth. Both HIU ablation and the A-mode imaging ultrasound transducers were mounted on the distal end of the transducer. The HIU transducer is a single element, 3.5 x 5.0 mm, side-facing PZT-4 piezoceramic crystal (EBL Products Inc.; East Hartford, CT), with a frequency of 6.4 MHz, mounted with air backing to maximize power output efficiently in continuous wave (CW) mode. The A-mode imaging transducer (PZT5H, 3 mm x 3 mm, tungsten-loaded, epoxy-backed) was operated in pulsed-echo mode and mounted immediately proximal to the HIU transducer. A-mode images were displayed in real-time on an oscilloscope (Hewlett-Packard 54600A; Palo Alto, CA) (Figure 2). The transducer assemblies were encapsulated within a thin-walled polyester balloon designed to maintain contact with the myocardium, and to cool the transducers with internal irrigation. Continuous closed-loop internal irrigation with degassed water is maintained at 50 ml/min with a peristaltic pump. A radio-opaque “S/Z” marker for determining catheter rotational orientation under fluoroscopy is located on distal end of the catheter (Figures 1 and 3A). The current prototype catheter is not steerable, but is advanced through a17 Fr steerable sheath (MedPass International; Gloucester, United
Kingdom) for manipulation within the epicardial space.

HIU ablations (6.4 MHz, continuous wave, 60 seconds) were programmed using a function generator (Agilent 33220A; Santa Clara, CA). Power is generated by a power amplifier (ENI 240L; Rochester, NY), and monitored using a power meter (Bird Technologies 4391A; Solon, OH).

**In-Vivo Ablation**

Female farm swine (40-50 kg) were intubated and underwent general anesthesia with inhaled isoflurane 2-3%. Coronary angiography was performed via right femoral arterial access, and subxyphoid percutaneous pericardial access was obtained using the method described by Sosa and colleagues\(^\text{10}\). After serial dilation, a 17 Fr steerable sheath was advanced into the pericardial space and the HIU catheter was advanced through the sheath into the pericardial space. The catheter’s fluoroscopic marker (Figure 3A) and A-mode US (Figure 2) were used to orient the rotation of the sheath so as to orient the ablation beam orthogonal to the epicardial surface.

Left coronary angiography was performed via right femoral arterial access to define the coronary anatomy. Lidocaine 50-100 mg IV was administered prior to ablation to decrease the risk of ventricular arrhythmias. In 10 normal swine, HIU ablation was performed for 60 seconds at 15, 20 and 30 W over areas of LV epicardium at least 1 cm apart, avoiding delivering lesions near the coronary arteries. In two additional swine, HIU sonication was applied directly over the left anterior descending (LAD) and left circumflex (LCX) coronary arteries at 20 W and 30 W, respectively, for 60 seconds each. Coronary angiography was performed before, during, and after sonication to assess for coronary flow, spasm, and thrombus (Figure 3B).

As a control, five swine underwent epicardial RF ablation using an externally irrigated (30 cc/min) ablation catheter (Thermocool, Biosense-Webster; Diamond Bar, CA) via an Agilis
steerable sheath (St. Jude Medical; St. Paul, MN) set to continuous suction to evacuate irrigation fluid from the pericardial space. RF ablation was started at 25 W, with upwards titration of power to achieve a >10 Ω impedance drop.

At the end of each study, 10 g of 2,3,5-Triphenyl-2H-tetrazolium chloride (TTC) dissolved in 50 ml normal saline was injected intravenously for staining to enhance lesion visualization. Hearts were excised intact, and fixed in 10% formalin for one week. After formalin fixation, hearts were sectioned and imaged in short axis slices of 2.5 mm thickness for gross pathology. Lesion slices were further sectioned at a thickness of 10 μm, and stained with hematoxylin and eosin (H&E) and Masson’s trichrome for histologic analysis.

This protocol was approved and monitored by the University of California San Francisco Institutional Animal Care and Use Committee under guidelines set forth by the Association for the Assessment and Accreditation of Laboratory Animal Care.

Statistical Analysis
Lesions were measured in three dimensions using ImageJ software (National Institutes of Health; Bethesda, MD), and lesion volume was calculated using the ellipsoid formula for HIU lesions

\[(2/3 \times \pi \times D \times (L \times W) /2)\] and half-ellipsoid formula \[(2/3 \times \pi \times D \times (L \times W) /4)\] where D = lesion depth (from epicardium to endocardium), L = length (along apical-basal dimension), and W = width (along septal-lateral dimension) for RF lesions. These equations have previously been used for assessment of RF\(^7\text{-}^9\) and ultrasound\(^15\) lesion volumes, respectively. Data is presented as mean ± SD.

After performing a generalized estimating equation (GEE) regression with clustering on pigs, fitted mean values of lesion characteristics were estimated using standardization, and individual HIU power groups were compared to RF using Sidak-adjusted p-values to account for
multiple comparisons. P-values were two-sided, and p < 0.05 was considered significant.

Results

A-Mode Ultrasound

In a pilot, open-chest study, the HIU transducer was visually rotated to aim orthogonal to the epicardium, and optimal A-mode tracings were recorded (Figure 2A). The catheter was then rotated 180° to aim directly away from the epicardium and toward the surrounding mediastinum and lung (Figure 2B). Because lung leads to multiple ultrasound reverberations, the difference in A-mode profile between epicardial myocardium and lung was readily apparent. These A-mode profiles were used to guide catheter rotation during closed-chested, in-vivo ablations.

In-Vivo Ablation

Percutaneous subxyphoid pericardial access was obtained with the steerable sheath and HIU catheter in 12 HIU-treated pigs, and with the Agilis sheath and Thermocool catheter in five RF-control pigs without complications. The radiopaque “S/Z” marker was easily visualized under fluoroscopy (Figure 3A), and used to guide catheter rotation, which was further refined by rotation to the optimal A-mode profile (Figure 2A). HIU lesions were applied at 15 W (n=12), 20 W (n=17), and 30 W (n=20) to areas of normal myocardium. RF lesions (n=22) were delivered with a power of 28.3 ± 6.7 W, starting impedance of 138.3 ± 34.1 Ω, and nadir impedance of 118.4 ± 29.4 Ω, resulting in a mean impedance drop of 19.8 ± 9.8 Ω (14% drop). Lesion depth, epicardial sparing, and volume at all three HIU powers and RF are shown in Figure 4, with characteristic lesions shown in Figure 5.

Depth and volume of HIU lesions demonstrated a direct dose-response relationship with power (Figure 4A and 4C, p < 0.0001 for heterogeneity). HIU lesion depth at all powers and HIU lesion volume at 20 W and 30 W (p < 0.0005 for all comparisons) were significantly greater than
RF, with 30 W demonstrating deepest and largest lesions (12.0 ± 4.2 mm HIU vs 4.7 ± 4.0 mm RF; 225.0 ± 102.9 mm³ HIU vs 57.0 ± 108.8 mm³ RF). HIU epicardial sparing demonstrated an inverse dose-response relationship with power (Figure 4B, p < 0.0001), was greater than RF at each HIU power level (p < 0.0001 for each comparison), and maximal at 15 W (4.2 ± 1.6 mm vs 0.1 ± 0.2 mm by RF).

**Lesions Over Coronary Arteries**

Angiography performed during and after delivery of HIU lesions over the coronary arteries demonstrated Thrombolysis in Myocardial Infarction (TIMI) grade III flow, with no coronary spasm (Figure 3B). At the end of each procedure, the left coronary system remained patent.

Gross pathology, and H&E- and Masson’s trichrome-stained sections of lesions made over coronary arteries demonstrated no thrombosis or damage to media or intima (Figure 6). Some lesions delivered over coronary arteries (69%) demonstrated disruption of epicardial fat, suggesting acoustic energy absorption by fat. In a subset of these (44%), disruption was noted to also involve the vessel adventitia (Figure 6B and C). The thickness of epicardial fat overlying these lesions was 3.6 ± 1.6 mm. In all sections, a lesion characterized by myocardial disruption with contraction band necrosis was noted deep to the coronary arteries (Figure 6B), verifying effective HIU energy delivery through the epicardial fat and coronary arteries. Histologic findings are detailed in Table One.

**Discussion**

We have developed a 14 Fr, internally-irrigated HIU ablation catheter, and demonstrated its capacity to make lesions that are deeper, larger, and associated with much greater epicardial sparing than RF energy. Overall, 20 W HIU demonstrated the optimal balance of depth (11.6 ± 3.8 mm) and epicardial sparing (3.2 ± 1.7 mm). HIU was also able to create deep lesions through
epicardial fat and coronary arteries without acute coronary injury. These characteristics make HIU an attractive energy source for VT ablation in patients with NICMP, who are likely to have epicardial or mid-myocardial VT isthmuses, particularly when scar is located beneath epicardial fat or coronary arteries. HIU may also be useful in patients with ischemic CMP who have experienced VT recurrence despite ablation with RF. A-mode guidance allows directed targeting of cardiac tissue away from the lungs and phrenic nerve; the distal irrigated balloon facilitates conduction of ultrasound to the cardiac tissue, and promotes epicardial sparing by cooling the epicardial surface.

HIU has previously been investigated for catheter ablation of atrial fibrillation (AF), both from a surgical epicardial approach and using a balloon-based endocardial platform. However, HIU’s depth of ablation led to unacceptably high rates of atrio-esophageal fistulas from the endocardial approach, leading to eventual abandonment of this technology for AF ablation. One prior study has assessed the utility of HIU ablation in the ventricle, creating epicardial lesions in a swine model, although the lesions were created in an open-chest model and not compared to RF ablation. Our study demonstrates potential clinical benefits of HIU VT ablation by performing catheter-based, closed-chested ablation via percutaneous sub-xiphoid pericardial access similar to clinical practice. It should be noted that irrigated RF ablation in our study was performed with a commonly used, commercially-available catheter, and at power levels and impedance drops typical of aggressive clinical ablation. RF lesion sizes in our study were comparable to those seen in other in-vivo studies.

The main limitation of our study is that in-vivo lesions were assessed acutely, and swine were not survived to assess lesion development over time, primarily due to cost limitations. Prior to development for clinical use, HIU lesions, particularly over coronary arteries, should be
studied in survival studies to assess chronic lesion sizes, and delayed effects on coronary arteries. The aforementioned open-chested swine HIU ablation study assessed chronic effects of ablation over coronary arteries after two to eight weeks survival, and found that, although there was some progression of coronary pathology over time, overall 64% of lesions were free of significant injury\textsuperscript{15}. Furthermore, HIU ablation characteristics in areas of myocardial scar should be investigated, as acoustic characteristics of healthy and scarred myocardium may differ.

Future generations of this HIU catheter will decrease catheter diameter from current 14 Fr, and incorporate steerability (currently positioned using steerable sheath) to allow assessment of endocardial ablation. Geometric focusing of the HIU beam may further improve epicardial and coronary sparing. Based on HIU lesion depth demonstrated, endocardial HIU may also allow ablation of epicardial VT from an endocardial approach, thus obviating the need for higher-risk pericardial access. If endocardial lesions are similar to the epicardial lesions demonstrated here, HIU ablation may also allow ablation of deep septal VTs, which are currently challenging to ablate using RF from either side of the interventricular septum\textsuperscript{20,21}.

In conclusion, we have developed an internally irrigated, side-facing, epicardial HIU catheter, capable of making large, deep lesions with sparing of epicardial tissue. Dose ranging studies showed that 20W lesions had the best balance of depth of penetration and epicardial sparing. Lesions were effective even through epicardial fat, and direct application over coronary arteries led to effective lesions without intimal coronary injury. Further development of this catheter may lead to a viable alternative to RF ablation.

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**Conflict of Interest Disclosures:** None

**References:**


**Table 1:** Histologic analysis of lesions over coronary arteries

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<tr>
<th></th>
<th>Fat disruption</th>
<th>Adventitial disruption</th>
<th>Intimal disruption</th>
<th>Epicardial Fat Thickness (mm, mean ± SD)</th>
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<td>LAD (n = 12 lesions)</td>
<td>8 (67%)</td>
<td>6 (50%)</td>
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<td>3.9 ± 1.7</td>
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<tr>
<td>LCX (n = 4 lesions)</td>
<td>3 (75%)</td>
<td>1 (25%)</td>
<td>0 (0)</td>
<td>3.3 ± 1.3</td>
</tr>
<tr>
<td>Total (n = 16 lesions)</td>
<td>11 (69%)</td>
<td>7 (44%)</td>
<td>0 (0)</td>
<td>3.6 ± 1.6</td>
</tr>
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LAD - left anterior descending coronary artery; LCX - left circumflex coronary artery; SD - standard deviation
Figure Legends:

Figure 1: HIU ablation catheter tip built upon 14 Fr nylon catheter housing incorporates a fluoroscopy marker, A-mode imaging transducer, and internally-cooled HIU ablation transducer. HIU, high-intensity ultrasound.

Figure 2: A-mode ultrasound displaying intensity of acoustic reflections (y-axis) over depth (x-axis). A: Catheter pointed toward epicardium shows thin, mildly echogenic myocardial reflection (arrow) followed by anechoic blood (bracket). B: Catheter pointing away from heart shows multiple, highly echogenic reflections of lung tissue.

Figure 3: Fluoroscopy of in-vivo HIU ablation over basal anterior LV (A), and coronary angiography performed during ablation over LCX coronary artery (B). A: Radiopaque “S” (white arrow) orientates ablation away from image intensifier and toward LV anterior wall. B: Coronary angiography during HIU ablation directly over LCX demonstrates normal flow without spasm or thrombus. HIU, high-intensity ultrasound, LV, left ventricle; LCX left circumflex.

Figure 4: Comparison of HIU (15, 20 and 30 W) and RF lesion depth (A), epicardial sparing (B), and volume (C). Box denotes denotes 25th and 75th percentiles, middle line denotes median, bars denote range. p < 0.0001 by one-way ANOVA for all comparisons, ns, not significant; ** p < 0.005 and *** p < 0.0001 compared with RF by Sidak-adjusted multiple comparisons test. HIU, high-intensity ultrasound; ANOVA, analysis of variance; RF, radiofrequency
**Figure 5:** Representative HIU and RF epicardial lesions. TTC-stained cross-sections of LV myocardium shown with epicardial surface on top.

HIU, high-intensity ultrasound; RF, radiofrequency; TTC, 2,3,5-Triphenyl-2H-tetrazolium chloride; LV, left ventricle.

**Figure 6:** HIU ablation over LAD (20 W, A-C) and LCX (30 W, D-F) demonstrates myocardial lesion through epicardial fat and coronary artery on gross pathology (A, D). Masson’s trichrome (B, E) and H&E (C, F) at very low and low (bottom panels of E and F) magnifications demonstrate mild fat disruption with no abnormalities of the intima or media. Mild disruption of the coronary adventitia was noted around the LAD (B), but not the LCX. Ablation performed in direction of the black arrows.

HIU, high-intensity ultrasound; LAD, left anterior descending coronary artery, LCX, left circumflex coronary artery, H&E, hematoxylin & eosin

**Figure 7:** Schematic illustration to scale of mean lesion depth, width, and epicardial sparing of HIU and RF lesions. HIU and RF catheters shown to scale.

HIU, high-intensity ultrasound; RF, radiofrequency
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