Contrast in Intracardiac Acoustic Radiation Force Impulse Images of Radiofrequency Ablation Lesions

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Stephanie A. Eyerly¹, Tristram D. Bahnson², Jason I. Koontz², David P. Bradway¹, Douglas M. Dumont¹, Gregg E. Trahey^{1,3}, and Patrick D. Wolf¹

Abstract

We have previously shown that intracardiac acoustic radiation force impulse (ARFI) imaging visualizes tissue stiffness changes caused by radiofrequency ablation (RFA). The objectives of this in vivo study were to (1) quantify measured ARFI-induced displacements in RFA lesion and unablated myocardium and (2) calculate the lesion contrast (C) and contrast-to-noise ratio (CNR) in two-dimensional ARFI and conventional intracardiac echo images. In eight canine subjects, an ARFI imaging-electroanatomical mapping system was used to map right atrial ablation lesion sites and guide the acquisition of ARFI images at these sites before and after ablation. Readers of the ARFI images identified lesion sites with high sensitivity (90.2%) and specificity (94.3%) and the average measured ARFI-induced displacements were higher at unablated sites ($11.23 \pm 1.71 \mu\text{m}$) than at ablated sites ($6.06 \pm 0.94 \mu\text{m}$). The average lesion C (0.29 ± 0.33) and CNR (1.83 ± 1.75) were significantly higher for ARFI images than for spatially registered conventional B-mode images ($C = -0.03 \pm 0.28$, $CNR = 0.74 \pm 0.68$).

Keywords

acoustic radiation force impulse imaging, cardiac radiofrequency ablation, intracardiac echocardiography, electroanatomical mapping

Introduction

Over the past decade, transcatheter cardiac ablation (TCA) procedures for treatment of supraventricular arrhythmias have become routine in hospitals around the world.¹ TCA aims to restore normal sinus rhythm by destroying or electrically isolating arrhythmogenic tissue with radiofrequency ablation (RFA) lesions. Nontransmural ablation lesions or unablated gaps in isolation lines continue to conduct arrhythmogenic wavefronts. Predicting RFA lesion size, transmurali-

¹Department of Biomedical Engineering, Duke University, Durham, NC, USA

²Duke Center for Atrial Fibrillation, Duke Heart Center, and Clinical Cardiac Electrophysiology Section of the Division of Cardiovascular Medicine, Duke University, Durham, NC, USA

³Department of Radiology, Duke University Medical Center, Durham, NC, USA

Corresponding Author:

Patrick D. Wolf, Department of Biomedical Engineering, Duke University, 136 Hudson Hall, Durham, NC 27708, USA.

Email: patrick.wolf@duke.edu

Figure 1. Example of a CARTO XP™ chamber geometry map of a canine right atrium (RA). ICE = intracardiac echocardiography; RFA = radiofrequency ablation.

and line contiguity based on delivery parameters, such as radiofrequency (RF) duration and power, has been unreliable because variable convective cooling from blood flow at the ablation site and the instability of the electrode–tissue contact in the beating heart significantly affect lesion formation.^{2–6} Also, there is currently no widespread clinical imaging method to intraprocedurally visualize and evaluate RFA lesions. Reported rates of arrhythmia recurrence post-TCA are typically around 20%, and studies have attributed arrhythmia recurrence to incomplete lesions or electrical conduction through unablated gaps in isolation lines.^{7–11} Direct visualization of RFA lesions could improve the efficacy of TCA procedures by providing an intraprocedure method to confirm RFA lesion size and transmuralty.^{1,4,8}

Several tracking and imaging modalities are currently used in electrophysiology (EP) labs to guide TCA; however, none can be used to differentiate ablated from unablated myocardium. Fluoroscopy is used to visualize catheters in the body but does not provide the soft tissue resolution needed to visualize the cardiac anatomy or RFA lesions.¹² Intracardiac echocardiography (ICE), or catheter-based B-mode imaging, is frequently used to visualize the cardiac anatomy and ablation electrode–tissue contact in real time, but the acoustic contrast between ablated and unablated tissue is insufficient for lesion characterization.^{13–19}

Electroanatomical mapping (EAM) systems are the current clinical standard for guiding RFA lesion placement. The CARTO XP (Biosense Webster, Diamond Bar, CA, USA) EAM system uses magnetic-field-based tracking technology to locate catheter tip position and orientation in the heart.^{1,20,21} With this system and others like it, a three-dimensional (3-D) cartoon geometry of the heart chamber is interpolated from a point catalog of acquired mapping catheter positions (NaviStar™; Biosense Webster, Diamond Bar, CA, USA). RF-delivery sites are marked during ablation in the map geometry. The position of the ICE imaging catheter (SoundStar™; Biosense Webster, Diamond Bar, CA, USA) is also tracked in the system, and the projected imaging plane orientation is shown in the chamber geometry. An example of a CARTO XP geometry is shown in Figure 1. EAM is an essential and widely used clinical tool for guiding and mapping ablation

lesion locations during TCA procedures; unfortunately, these tracking systems can only represent RFA treatment locations within the geometric cartoon and cannot provide direct visual confirmation of RFA lesion size and transmuralty within the myocardium.

Over the past decade, radiation-force-based elastography methods have been investigated for the visualization of stiffness changes at ablation sites in liver, kidney, and cardiac tissues.^{18,19,22-27} In these tissues, RF-induced tissue heating causes irreversible intracellular and contractile protein denaturation, making the ablated tissue stiffer than the surrounding untreated tissue.^{25,28,29}

Acoustic radiation force impulse (ARFI) imaging is an ultrasound-based imaging technique that creates two-dimensional (2-D) images of relative tissue elasticity.^{19,30-34} To create an ARFI image, a sequence of short-duration radiation force impulses is applied over a lateral field of view (FOV) and the tissue response is monitored with conventional ultrasound scan lines. The tissue displacement is typically on the order of 10 μm and is calculated using delay estimator methods.^{35,36} Assuming the soft tissue can be considered a linear, elastic, isotropic medium, the calculated radiation-force-induced displacement magnitude is inversely proportional to the tissue stiffness.^{32,33,37-40} We have previously shown that 2-D ARFI images can visualize the relative tissue elasticity changes induced by RFA heating in cardiac tissue *in vitro*.^{17,41} Fahey et al. and Hsu et al. demonstrated the feasibility of ICE-based ARFI imaging for *in vivo* intracardiac RFA lesions assessment, and Eyerly et al. showed areas of conduction disturbance or block (mapped with EAM) around linear RFA sites were consistent with reader detected RFA lesion in ARFI images.^{18,19,42}

A quantitative analysis of both the range of ARFI-induced displacements and the contrast between unablated and ablated myocardium *in vivo* has not yet been performed. One reason for this is the lack of a dependable method to confirm the presence of a lesion within the 2-D imaging plane. While an examination of the tissue pathology would be the ideal gold standard for identifying RFA lesions, registering the 2-D ARFI imaging plane location and orientation to the *ex vivo* pathology would result in substantial misregistration error and would compromise the accuracy of the experiment.

In this study, ablated sites as determined by an EAM system were interrogated with ARFI imaging to determine the presence or absence of a region of increased stiffness. Image plane registration to ablated sites was provided by a commercial CARTO XP EAM system; the imaging plane of an ICE ultrasound catheter (SoundStar) was aligned to the magnetically determined location of the ablation catheter tip during RF energy delivery. Based on this gold standard, the sensitivity and specificity of reader detected RFA lesions in the ARFI images were determined, the range of measured ARFI-induced displacements for unablated and ablated sites was characterized, and RFA lesion contrast (C) and contrast-to-noise ratio (CNR) were measured.

Method

Multi-Modality Imaging System

ARFI imaging sequences. An ACUSON S2000 ultrasound scanner (Siemens Healthcare, Issaquah, WA, USA) was software-modified to implement 2-D ARFI beam sequences from a standard 64-element SoundStar ICE catheter (Biosense Webster, Diamond Bar, CA, USA). Images were acquired with transmit and receive center frequencies of 6.15 MHz and with a 1.5 cm focus ($F/\# = 2.14$).

At the start of the imaging sequence, a 90° lateral FOV conventional B-mode image was acquired. Next, 10 high-intensity ARFI “priming” pulses were transmitted. Radiation-force pulses transmit high-intensity acoustic waves forward into the tissue as well as backward into the transducer matching layer. The absorption of this mechanical energy generates a force that bends

the flexible imaging catheter in the opposite direction of the radiation force impulse; this transducer “kick-back” is initially nonlinear and difficult to remove from ARFI displacement estimations.¹⁹ The 10 priming pulses were fired before the ARFI pulses, so any remaining kick-back motion was linear and could be effectively removed from the ARFI displacement estimations with the motion filtering technique described in the Image Processing section.¹⁹ The last portion of the imaging sequence was a 2-D ($\sim 54^\circ$ FOV) ARFI image, consisting of 42 spatially interleaved equispaced ARFI locations. Each lateral ARFI location was imaged prior to ARFI excitation with 10 scan lines at a pulse repetition frequency (PRF) of 9.67 kHz. These “pre-push” lines were used for motion filtering during image processing. The location was also interrogated with 10 scan lines following the ARFI excitation to monitor the ARFI-induced tissue response. The full frame imaging sequence took ~ 92 ms to complete and was within regulatory limits for mechanical index ($MI < 1.7$) and transducer surface heating ($< 4.0^\circ\text{C}$).⁴³

ARFI imaging–EAM system integration. The S2000 was integrated with a CARTO XP EP Navigation EAM System that was modified with a custom CARTOSound module (Biosense Webster Software Development, Tirat Carmel, Israel). This integration spatially registered the 2-D ARFI imaging plane into the chamber geometry. The surface electrocardiogram (ECG) was acquired using an Octal Bio Amp (ADInstruments, Milford, MA, USA) and recorded using LabChart 7.0 data acquisition software (PowerLab ADInstruments, Milford, MA, USA).

RFA lesions remain stiff throughout the cardiac cycle, but unablated myocardium is more compliant when relaxed during diastole than when it is contracted during systole.^{18,19,35,42} Therefore, all ARFI images were acquired during diastole to maximize the stiffness contrast between RFA lesions and the surrounding unablated myocardium.^{18,19,35,42} Gating the image acquisitions to diastole also minimized the effects of bulk cardiac motion on the displacement estimations. A data channel was configured in the LabChart software to detect the ECG QRS complex (ventricular depolarization) and to deliver an impulse to the ultrasound scanner after a manually pre-programmed delay. This impulse was used to trigger the ARFI image acquisition in mid-diastole (typically a 300 to 500 ms delay).

Experimental Protocol

The animal study protocol was approved by the Duke University Animal Care and Use Committee and conformed to the Guide for the Care and Use of Laboratory animals.

In eight canines, a baseline point-by-point geometry of the right atrium (RA) was made with the ARFI imaging–EAM system. A guideline delineating the planned linear RFA-delivery site was drawn on the map geometry, and EAM-directed ARFI images of the pre-ablation tissue along the guideline were acquired before RFA delivery. A series of RFA lesions were delivered along the guideline using a catheter dragging technique to minimize potential lesion line discontinuities. As the line segments were created, catheter location sites along the segment were marked in the EAM geometry.⁴⁴ The ablation proceeded in two steps: (1) a line was created with an intentional gap of approximately 1 cm length and (2) the intentional gap was closed. RF energy delivery was applied for 30 to 90 s per line segment, and the ablation electrode tip was temperature controlled between 50°C and 60°C with a 30 W power cap. ARFI images were acquired after RFA using the EAM RFA markers to direct the imaging.

During image acquisition, the ablation catheter was removed from the FOV because the catheter tip blocked acoustic energy from reaching the myocardium. Also, the ICE catheter was positioned such that the endocardial border appeared near the focus (1.5 cm) and was as parallel to the transducer face as possible. This was done to maximize the induced displacement and to minimize depth-dependent energy delivery to the tissue.^{19,30,32,33} Any ARFI images with the endocardial surface outside the focal depth of field (DOF; above 0.5 or below 2.25 cm) were not

included in the statistical analysis. Images were also excluded if the endocardial border was at an angle greater than 50° from parallel because the depth-dependent difference in acoustic energy delivery could potentially be mistaken for RFA treatment.³³

After the procedure, the heart was removed, photographed, and the RA was examined to confirm a contiguous line of RFA lesions.

ARFI Image Processing

The ARFI image processing was completed in MATLAB (The MathWorks, Inc., Natick, MA, USA) after the experimental procedure. The 2-D ARFI images were formed using the normalized cross-correlation time-delay axial displacement estimation method outlined by Hsu et al.¹⁹ A normalized cross-correlation coefficient (NCCC) was calculated for each post-ARFI-excitation displacement estimation ($n = 10$ post-tracking scan lines) at each pixel location. The NCCC quantified the quality of the phase-matching between the post-ARFI scan lines and the last pre-ARFI line (reference line). A low NCCC signified greater phase-mismatch during the cross-correlation and indicated a poor displacement estimation. Pixels with poor displacement estimates were removed from the ARFI images by thresholding the median NCCC ($n = 10$) at each pixel location to include only pixels with values greater than 0.80. This process eliminated most of the displacement estimates from image locations in the blood in the RA.

The ARFI-induced displacement measurements were motion-filtered with a quadratic extrapolation model to reduce the effects of axial bulk physiological motion and catheter rebound on the displacement estimates.^{19,45,46} Remaining pixels in the blood or beyond the myocardium were masked from the image by removing individual pixels locations where (1) the measured displacement estimation was $>50 \mu\text{m}$ or (2) the standard deviation of the displacement measurements through the tracking time was greater than $20 \mu\text{m}$. The B-mode image and maximum ARFI-induced displacement measurements from the post-ARFI-excitation scan lines were scan-converted, plotted at each pixel location, and color-coded to form the ARFI image (bilinear interpolation scan conversion, 0.019 mm axial by $\sim 1.33^\circ$ lateral kernel pre-scan conversion, $0.05 \times 0.05 \text{ mm}$ pixel size post-scan conversion). The ARFI image pixel color scale was manually adjusted to increase the visual contrast and reduce saturation in the final displayed image. The upper limit of the displayed displacement range for all images was between 7.5 and $15 \mu\text{m}$. The lower limit was always $0.0 \mu\text{m}$.

ARFI Image Review for the Presence of RFA Lesion

Three readers reviewed the processed ARFI images for the absence or presence of RFA lesion in the myocardium at the imaging location, identifying lesion as at least one area (larger than approximately $0.5 \times 0.5 \text{ mm}$) of low relative ARFI-induced displacement. The ARFI images were randomized, and each reader was blinded to the electroanatomical maps, canine subject, and stage of ablation. The majority assessment was used as the final classification of the image, and the level of agreement between the readers was quantified with a kappa coefficient. In the EAM maps, the ARFI imaging plane transecting any part of a 4 mm diameter spherical RFA marker was used to indicate the presence of RFA lesion at the imaging location. Each image was categorized in a 2×2 contingency table and the sensitivity and specificity were calculated.

Contrast Performance Analysis of ARFI-Induced Displacements in Unablated and Ablated Myocardium

A reader was blinded to the ARFI images and used the maps of the RFA markers and ICE-fan projection to classify each location as imaging: No Lesion (fan did not intersect a marker),

Noncontiguous Lesion (fan partially intersected a marker line), or Contiguous Lesion (fan completely intersected a marker line). Images that partially intersected an RFA marker line were used for the contrast analysis. For these images, the reader manually selected an ablated and unablated area in the myocardium on the B-mode image that matched the marker intersection of the fan in the electroanatomical map. This selection dictated the location of two (one ablated, one unablated) 1×1 mm (20×20 pixels) regions of interest (ROIs) in the spatially registered ARFI image. For the ARFI images of No Lesion and Contiguous Lesion, a 2×1 mm (40×20 pixels) ROI was taken from the center of the FOV. Each image contributed the same number of data points (800 total pixels) to the analysis. The 1 mm axial depth for the ROI was chosen because the atrial myocardium was typically between 1.5 and 2 mm thickness. All ROI were taken 0.25 mm below a manual trace of the endocardial surface to insure the measurement region was within the myocardium. The surface trace was made using only the B-mode image. The mean and standard deviation of the maximum ARFI-induced displacement were calculated for the pixels in each ROI.

A repeated-measures analysis of variance (ANOVA) to test for an RFA lesion effect was performed on the ROI-measured displacement values. This statistical model was used because multiple ROI were selected in each animal.

$$C = \frac{\mu_{UA} - \mu_A}{\mu_{UA}}, \quad (1)$$

$$CNR = \frac{|\mu_{UA} - \mu_A|}{\sqrt{\sigma_{UA}^2 + \sigma_A^2}}. \quad (2)$$

The C and CNR were calculated for each image with paired ablated and unablated ROI using Equations 1 and 2, where μ_{UA} and μ_A are the means of the measured ARFI-induced displacement in the unablated and ablated ROI, respectively, and σ_{UA}^2 and σ_A^2 are the variances for the respective ROI.^{33,47,48} The C and CNR were also calculated for the mean signal amplitude in the spatially registered ROI in the B-mode images. A repeated-measures ANOVA for lesion presence was performed for the paired ROI-measured displacement means. Additional repeated-measures ANOVA tests were performed for the C and CNR values in the ARFI and B-mode images. A one-tailed paired *t*-test was used to determine if there was a significant positive difference in the mean C and CNR of lesion in the ARFI images compared with the B-mode images.

Bulk Motion Artifacts

The motion filtering technique described previously reduced the effects of bulk axial motion on the ARFI-induced displacement estimates, but large motion artifacts occurred if an acquisition was mistimed to acquire partially in systole or during an irregular heartbeat such as a premature ventricular contraction (PVC). The ARFI imaging sequence for this study acquired A-lines at temporally interleaved lateral locations; therefore, if substantial lateral or axial motion occurred during the acquisition, the endocardial surface was discontinuous or “jagged” in the B-mode image. Motion artifacts also presented a distinct “streaking” pattern in the displacement estimates that corresponded to the tracking of the bulk cardiac motion instead of the ARFI-induced displacements. ARFI images exhibiting such motion artifacts or low NCCCs (more than 50% of the displacement estimates having NCCCs < 0.80 within the myocardium) were not included in the statistical analysis (28 of 247 total images).

Results

Identification of RFA Sites with ARFI Imaging

An examination of the ex vivo pathology determined that individual lesions were typically 4 to 8 mm in diameter, and the locations of the RFA line were consistent with the EAM representations. The post-mortem pathological examinations confirmed complete linear RFA was achieved in seven out of the eight canine subjects.

A small (<5 mm) unablated gap in an otherwise contiguous RFA line was found in a single subject; ARFI images from each stage of ablation as well as the corresponding electroanatomical maps and pathology for this subject are shown in Figure 2. RF-delivery sites are shown in the electroanatomical maps (column 1) as 4 mm diameter red spheres. Before RFA, the myocardium exhibited relatively high ARFI-induced displacement, color-coded by the red-orange spectrum of the color bar. Post-RFA (Figure 2-B3, C3, and D3), the measured ARFI-induced displacements were lower at the RFA-treated locations (color-coded as blue-green), indicating an increase in the tissue stiffness and the presence of lesion. There is no notable change in the myocardium in the B-mode ICE images. An ARFI image of the incomplete linear ablation (Figure 2-B3) showed an unablated gap in the lesion line consistent with the gap in RFA markers (dark red spheres, yellow plane B in Figure 2-E and F) at the imaging location observed in the EAM. Consolidating RFA (white arrow panel E-F) attempted to close this gap (light red spheres in Figure 2-E), and complete linear RFA is seen at the superior imaging location in Figure 2-C3 (cyan plane C in Figure 2-E and F). Figure 2-D3 is an ARFI imaging showing a small unablated gap (black arrow panel E-F) at an inferior imaging location (navy plane D in Figure 2-E and F); the observation of this gap is consistent with the unablated gap in the pathology image (Figure 2-F) despite the presence of the RFA markers in EAM.

The ROI used for the measured ARFI-induced displacement calculations are shown as white boxes in the ARFI images. The ROI in Figure 2-3A (unablated), 3B (paired: ablated and unablated), and 3C (ablated) are consistent with lesion sites marked in EAM, while the gap consistent with pathology in Figure 2-D3 misrepresents an ablated ROI due to the appearance of a contiguous line of markers in the EAM.

A total of 219 ARFI images were read for the presence of lesion. Table 1 shows the categorization of the 219 ARFI images. Readers of the ARFI images identified RFA lesion sites with a sensitivity of 90.2% and a specificity of 94.3% and showed substantial agreement ($\kappa = 0.73$).

Contrast of Maximum ARFI-Induced Displacements in Lesion and Unablated Myocardium

Figure 3 is a plot of the mean and standard deviation of all the ARFI-induced displacement measurements in unablated and ablated canine myocardium.

Table 2 summarizes the results of the statistical analysis. The mean (all images, $n = 219$) measured ARFI-induced displacement was lower in ablated than unablated ROI ($n = 143$ unablated, $n = 152$ ablated). A repeated-measures ANOVA indicated the presence of RFA lesion had a significant effect ($p = 0.0001$) on the measured displacements, whereas the canine subject effect was not significant ($p = 0.11$).

For images that contained both RFA lesion and unablated myocardium ($n = 76$ paired images), the mean-measured ARFI-induced displacement was lower for the ablated ROI. A repeated-measures ANOVA determined that the presence of RFA lesion had a significant ($p = 0.0004$) effect on the measured displacement means and the canine subject did not at an alpha value of 0.01 ($p = 0.03$).

Figure 2. Column 1: Electroanatomical maps of canine right atrium (RA). The ultrasound imaging plane was steered to transect the radiofrequency ablation (RFA) lesion sites (red spheres, 4-mm diameter). Columns 2 and 3: B-mode and acoustic radiation force impulse (ARFI) images were acquired before RFA (row A), after noncontiguous RFA (row B), and after linear ablation (rows C and D). The ARFI images exhibit lower ARFI-induced displacement at the RFA ablation sites. The regions of interest (ROIs) used for mean ARFI-induced displacement measurements and the contrast and contrast-to-noise calculations (row B, paired only) are outlined in white. Color scale units are maximum ARFI-induced displacement away from the transducer in microns. Panel E: Epicardial surface traces at the imaging plane locations in electroanatomical mapping (EAM) for post-RFA (noncontiguous ablation = dark red spheres, linear ablation = light red spheres and white arrow). ARFI images (B = yellow, C = cyan, D = navy). Panel F: The approximate imaging planes from panel E manually traced on the post-mortem lesion pathology. ARFI image (row D) depicted an unablated gap consistent with the unablated gap (black arrow) observed in the pathology. TCA = transcatheter cardiac ablation.

Table 1. ARFI Imaging-Based Confirmation of RFA Lesion Sites in EAM (4 mm RFA Marker Diameter).

	ARFI Image Lesion Assessment		
	No RFA Detected	RFA Detected	Total
RFA marker location in EAM			
No RFA lesion	55	9	64
RFA lesion	6	149	155
Total	61	158	219

Sensitivity = 90.2%; Specificity = 94.3%; χ^2 test $p < 0.0001$. ARFI = acoustic radiation force impulse; RFA = radiofrequency ablation; EAM = electroanatomical mapping.

Figure 3. Boxplot of maximum acoustic radiation force impulse (ARFI)-induced displacements for region of interest (ROI) in unablated and ablated canine myocardium ($n = 219$ images). The center line represents the median ARFI-induced displacement measurement. The top and bottom edges of the box (shown in blue) are the 75th and 25th percent quartiles. The top and bottom whisker edges are the extreme values (covering 99.3% of the data), and the individually plotted crosses (shown in red) are statistical outliers. RFA = radiofrequency ablation.

Table 2 also presents the average C and CNR for the ARFI and B-mode images containing both unablated and ablated ROI. The average B-mode C and CNR were lower than the average ARFI image C and CNR. A one-tailed paired t -test indicated the C and CNR were significantly higher in the ARFI images than in the B-mode images ($p < 0.001$). A repeated-measures ANOVA determined the canine subject did not significantly affect the C and CNR for the ARFI ($p_C = 0.36$, $p_{CNR} = 0.72$) and B-mode ($p_C = 0.52$, $p_{CNR} = 0.73$) images.

The criteria described in the methods (low NCCC, unrealistic estimates) removed ARFI-induced displacement pixels from 33 ROI. Of these ROI, six had more than 5% of the pixels removed but no ROI had more than 17% of the pixels removed. No pixels were removed from the B-mode image ROI.

Discussion

In this study, ICE-based ARFI imaging successfully acquired in vivo images of the relative change in tissue elasticity associated with RFA. EAM precisely guided intraprocedure ARFI

Table 2. Mean and Standard Deviations of the ARFI Image ROI Displacements and Contrast Analysis for ROI in Unablated and Ablated Myocardium.

	Paired ^a Images		All ^b Images
	B-mode	ARFI ^c	ARFI ^d
Unablated myocardium (μm)	—	8.31 ± 4.27	11.23 ± 1.71
Ablated myocardium (μm)	—	5.11 ± 2.36	6.06 ± 0.94
Contrast (C) ^e	-0.03 ± 0.28	0.29 ± 0.33	—
Contrast-to-noise ratio (CNR) ^e	0.74 ± 0.68	1.83 ± 1.75	—

ARFI = acoustic radiation force impulse; ROI = regions of interest; ANOVA = analysis of variance.

^a76 paired images in eight canine subjects.

^b219 total images in eight canine subjects.

^c $n = 76$ unablated ROI, 76 ablated ROI; repeated-measures ANOVA, subject effect ($p = 0.03$, $F = 4.67$) and lesion effect ($p = 0.0004$, $F = 31.54$).

^d $n = 143$ unablated ROI, 152 ablated ROI; repeated-measures ANOVA, subject effect ($p = 0.1$, $F = 2.6$) and lesion effect ($p = 0.0001$, $F = 47.21$).

^eRepeated-measures ANOVA of subject effect of ARFI image C ($p = 0.36$, $F = 1.12$), and CNR ($p = 0.72$, $F = 0.64$) and B-mode C ($p = 0.52$, $F = 0.89$) and CNR ($p = 0.73$, $F = 0.63$); one-tailed paired t -test for C ($p = 1.15\text{e-}8$) and CNR ($p = 7.54\text{e-}7$) between ARFI and B-mode images.

imaging to RFA lesion sites. A quantitative analysis showed ablated sites exhibited significantly lower ARFI-induced displacements than did untreated areas, and readers of the ARFI images identified RFA lesion sites with high sensitivity and specificity. The ARFI image C and CNR for lesion visualization were significantly higher than for conventional ICE imaging.

Qualitative Imaging

The measured ARFI-induced displacements are qualitative surrogates for relative tissue elasticity and do not quantify a material property.³⁸ Imaging the same location from a different angle, depth, or with different imaging parameters, such as frequency, focal depth, or $F/\#$, could result in different measured ranges of ARFI-induced displacement. This study determined the range of measurements and contrast for specific but clinically feasible imaging conditions: the myocardium was imaged (1) in diastole, (2) within a specific focal depth range (0.5–2.25 cm below the transducer), (3) from a nonoblique angle ($<50^\circ$), and (4) off-axis steering of the ultrasound beams was limited to $\pm 27^\circ$. It is also important to note that negative displacement amplitudes and amplitudes above $50 \mu\text{m}$ were removed from the ROI before calculating the mean displacement; these bounds contributed to the skewed distributions and nonnormal appearance of the plots in Figure 3.

Despite the lack of a quantitative measure, qualitative ARFI imaging is optimally suited to image discrete targets of differing elasticity, such as ablation lesions.⁴⁹ ARFI images have a spatial resolution that is dependent on the spatial density of the measurements. At 1.5 cm distance from the transducer, the imaging lines are 0.33 mm apart. We believe this spatial sampling is adequate to visualize gaps greater than 0.66 mm. However, the measured gap resolution is unknown at this time and its value will be a critical factor in determining overall clinical effectiveness. Shear wave elasticity imaging (SWEI) has also been shown to be useful for quantifying the shear wave velocity changes associated with the stiffness change caused by RFA lesions.^{38,39,50} However, shear wave speed calculation requires a spatial kernel that can result in lower resolution; it is not yet clear if the resolution of SWEI images is adequate for the assessment of lesion line gaps.⁴⁹

The contrast analysis in this paper demonstrated that ARFI images can differentiate RFA lesion from nonlesion. This ability could provide a useful tool for TCA procedure guidance, where exact quantification of the tissue properties is not necessary.

While the quantitative analysis presented in this paper showed that ablated regions exhibit lower measured ARFI-induced displacements, the development of a method to automatically detect RFA lesion based on the ARFI images would require additional investigation. Spatial normalization of the displacement measurements is being investigated to compensate for the acoustic energy attenuation through depth and at extreme steering angles.

Considerations for Clinical Translation

ICE-based ARFI imaging could be translated relatively easily to clinical practice because the equipment needed to implement this technology is already in use in TCA procedures. Therefore, it is not necessary to invest in expensive new equipment, and electrophysiologists do not need extensive new training because they currently use similar tools and techniques.

Diastolic imaging is necessary for successful ARFI imaging of lesions as most of the contrast between lesion and normal tissue disappears when the tissue stiffens during systole.^{42,51} Also, late diastole is the time of least intrinsic motion during the cardiac cycle. We manually set the post-QRS delay to start the imaging in late diastole; however, this delay had to be adjusted multiple times throughout the study to account for changes in heart rate. Two of the false-positive images (ARFI image reader detected lesion, no marker in EAM) were acquired before the RFA-delivery phase of the experiment and may have indicated low ARFI-induced displacement due to a poor gating delay. Mistiming of the acquisition due to intermittent variations in heart rate may have also contributed to the high number of images with motion artifacts. The development of a tool to adjust the gating delay in real time could potentially reduce the instances of motion artifacts. Shortening the acquisition time of the imaging sequence could also help reduce the effect of motion on the displacement estimates.

Imaging the myocardium with the transducer face parallel to the endocardium and at the center of the focal DOF provided the highest contrast ARFI images. Using these criteria, we were able to acquire in vivo a substantial number of high-quality ARFI images in the canine RA. While the development of sequences for additional focal depths would marginally increase the potential imaging DOF range, at focal depths beyond 2.0 cm ($F/\# > 3$, ICE transducer length = 7 mm) the ARFI push intensity becomes less focused and there is a substantial reduction in the resulting displacements.¹⁹ The restricted DOF made imaging some areas of the canine heart challenging and may limit the number of sites that can be imaged with contemporary ICE catheters during clinical TCA procedures. Fortunately, typical human atria are larger than canine atria, and catheter steering and positioning may be easier in the larger chambers. Further investigation is needed to evaluate how these limitations would restrict ARFI imaging in human patients. Significant technical advances to address these limitations, such as the development of an ARFI imaging optimized transducer or more flexible ICE catheter steering technology, would improve the likelihood of clinical translation.

ARFI images require multiple ultrasound scan lines at each ARFI-excitation location to monitor the tissue deformation and therefore cannot be acquired at the same high frame rate as B-mode. This combined with the need for diastolic imaging means that continuous display rate ARFI imaging for lesion evaluation is not possible. Accelerated ARFI imaging could allow the acquisition of multiple frames in a single beat, but any increase in the ARFI imaging acquisition rates must be accompanied by a consideration of increased acoustic exposure (MI and transducer face heating).

Due to the restricted DOF, ARFI imaging lesion evaluation in the left atrium (LA) would require a double transseptal puncture to position the ICE catheter across the atrial septum. While ICE imaging in the LA is not mandatory for TCA procedures, it is a safe and effective method used by many electrophysiologists to monitor RF delivery and the ablation catheter contact in

real time. In this study, ARFI images were acquired in the canine RA to avoid performing a double transseptal puncture; transseptal punctures are difficult in the smaller canine heart. While these results were obtained in the RA, it is expected that similar results would be found in the LA.

Considerations for EAM Guided ARFI Imaging

In this study, EAM proved indispensable for mapping RFA treatment sites and guiding the imaging plane. The RFA markers in EAM were treated as the gold standard for indicating lesion locations. This experimental paradigm was used because attempting to match the exact orientation and location of each imaging plane to the ex vivo pathology would risk substantial misregistration errors that would affect the accuracy of the lesion evaluations. One problem with using EAM as the gold standard is that the RFA markers only infer RFA delivery and EAM cannot visually confirm the presence or size of the actual lesion. Discrepancies between the actual pathological lesion configuration and the electroanatomical map, as seen in Figure 2, could have resulted in the incorrect classification (ablated vs. unablated) of the ROI in the ARFI images. These misclassifications likely affected the statistical analysis and the C and CNR calculations.

For example, the six false-negative sites in Table 1 could have been sites where the RF energy did not induce a high enough temperature for ablation despite the location marker; or the lesion could have been very small (<4 mm) due to poor electrode–endocardium contact. This was likely the case for the unablated gap seen in the subject presented in Figure 2. At six of the nine false-positive sites, the imaging plane was positioned within ~ 4 mm of a lesion marker. One of the eight was within ~ 8 mm. In these cases, the predetermined marker diameter of 4 mm in the EAM could have contributed to the misclassifications; in the pathology examination, some lesions were substantially larger (>8 mm) than the EAM marker diameter. Despite this potential for misclassification, expert reviews of the ARFI images were very consistent with the presence of the RFA markers in the EAM.

Study Limitations

In this study, the standard deviation of the image CNRs was relatively high. The CNR calculation for each individual image incorporated the mean and variance of the ARFI-induced displacements in the ROI. Ultimately, the displacement mean and variance for each unablated and ablated ROI were influenced by the position of the myocardium in the imaging DOF; the distance of the tissue from the focal depth as well as the angle of the myocardium directly affect the energy-delivery profile from the ARFI excitation and therefore the relative magnitude of the measured ARFI-induced displacements. The range of possible depths and angles was restricted in this study to minimize these influences on the displacement measurements, but there was still variation within these limits that may have contributed to the relatively high standard deviation for the CNR. Poor manual selection of the unablated and ablated ROI locations based on the EAM maps could also have affected the C and CNR calculations. Despite these effects, readers of the ARFI images identified RFA lesion sites with high sensitivity and specificity, empirically indicating successful lesion detectability.

It is also important to note that the displacement ranges, contrast, and CNR were calculated from the maximum ARFI-induced displacement measurements; an examination of the displacement at different time points after the ARFI excitation could potentially result in different values for measured displacement.^{33,39,45,52,53} Also, ARFI imaging of lesion borders can result in shear wave (off-axis mechanical wave propagation) reflections from lesion-tissue boundaries.³⁹ The potential effect of such interactions on the contrast for thin (1–3 mm) inhomogeneous viscoelastic atrial tissue with irregular ablation lesion borders was beyond the scope of this study.

In this study, the maximum ARFI-induced displacement was not compared for the same exact sites before and after ablation; although the pre- and post-ablation sites were not more than 4 mm apart. Therefore, stiffness inhomogeneity in the atrial tissue could be mistaken for RFA lesion in the ARFI images. Despite this possibility, in the healthy canine heart, it is expected that such inhomogeneities would be minimal.

Conclusion

An integrated ARFI imaging–EAM system was used to acquire in vivo ICE-based ARFI images of RFA locations. Readers of the ARFI images correctly identified RFA lesion sites, and ARFI-induced displacement was significantly lower for ablated myocardium than unablated myocardium. The C and CNR for ARFI images of Noncontiguous Lesion showed good contrast between the treated and untreated sites, while B-mode images of the same sites showed little contrast between the tissue types.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Trahey reports relevant patent application and ownership.

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