Three Potential Mechanisms for Failure of High Intensity Focused Ultrasound Ablation in Cardiac Tissue

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Background—High intensity focused ultrasound (HIFU) has been introduced for treatment of cardiac arrhythmias because it offers the ability to create rapid tissue modification in confined volumes without directly contacting the myocardium. In spite of the benefits of HIFU, a number of limitations have been reported, which hindered its clinical adoption.

Methods and Results—In this study, we used a multimodal approach to evaluate thermal and nonthermal effects of HIFU in cardiac ablation. We designed a computer controlled system capable of simultaneous fluorescence mapping and HIFU ablation. Using this system, linear lesions were created in isolated rabbit atria (n=6), and point lesions were created in the ventricles of whole-heart (n=6) preparations by applying HIFU at clinical doses (4–16 W). Additionally, we evaluate the gap size in ablation lines necessary for conduction in atrial preparations (n=4). The voltage sensitive dye di-4-ANEPPS was used to assess functional damage produced by HIFU. Optical coherence tomography and general histology were used to evaluate lesion extent. Conduction block was achieved in 1 (17%) of 6 atrial preparations with a single ablation line. Following 10 minutes of rest, 0 (0%) of 6 atrial preparations demonstrated sustained conduction block from a single ablation line. Tissue displacement of 1 to 3 mm was observed during HIFU application due to acoustic radiation force along the lesion line. Additionally, excessive acoustic pressure and high temperature from HIFU generated cavitation, causing macroscopic tissue damage. A minimum gap size of 1.5 mm was found to conduct electric activity.

Conclusions—This study identified 3 potential mechanisms responsible for the failure of HIFU ablation in cardiac tissues. Both acoustic radiation force and acoustic cavitation, in conjunction with inconsistent thermal deposition, can increase the risk of lesion discontinuity and result in gap sizes that promote ablation failure. (Circ Arrhythm Electrophysiol. 2012;5:409-416.)

Key Words: cardiac arrhythmias | ablation | high intensity focused ultrasound | acoustic radiation force | cavitation | thermal effect

High intensity focused ultrasound (HIFU) has become an attractive option for treatment of atrial fibrillation and other arrhythmias.1–7 HIFU can create rapid tissue modification in confined tissue volumes (as small as 20 mm3) without directly contacting the myocardium.2,8 Furthermore, HIFU has a unique capability to induce intramural lesions at various depths without affecting intervening tissues.2,8 However, HIFU has limitations, which stem from incomplete understanding of physiological mechanisms of HIFU energy deposition in the heart. In recent clinical trials using St. Jude’s Epicor HIFU ablation system and ProRhythm’s HIFU balloon ablation catheter, several complications were identified, including atrial-esophageal fistula, pulmonary embolism, and phrenic nerve damage.8–11

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When discussing the benefits and drawbacks of HIFU as a tool for cardiac ablation, it is important to note a few basic principles regarding ultrasound. Ultrasound is a mechanical wave involving periodic changes of local pressure and density at frequencies above 20kHz.12 Propagation and scattering of ultrasonic waves in biological tissue have been used for both diagnostic imaging and therapeutic applications. Unlike diagnostic ultrasound, which generally operates in a higher frequency band (eg, 5–30 MHz), therapeutic ultrasound, such as HIFU systems, often operates at lower frequencies (eg, 0.5–5 MHz) and uses higher acoustic energy to induce irreversible tissue changes.12 Typical HIFU transducers are designed with a strong geometric or electronic focus to concentrate acoustic energy in a cigar-shaped profile, with its length and width dependent on the transducer F-number and center frequency.13

High intensity focused ultrasound can produce effects in tissue through 3 primary mechanisms: mechanical, thermal, and cavitation (which is a special form of mechanical effects).12–15 When exposed to an acoustic field, tissue is
subjected to the acoustic radiation force or pressure associated with the gradient of the acoustic energy distribution in a medium. Temperature elevation during ultrasound application is dependent on a combination of both tissue properties, including thermal absorption coefficient and perfusion rate, as well as ultrasonic parameters such as acoustic intensity (or acoustic pressure) and exposure duration. HIFU ablation relies on achieving a thermal dose above a specific threshold to create coagulative necrosis, described by the critical cumulative equivalent minutes at 43°C. In addition to thermal effects, nonthermal effects, such as acoustic cavitation, also can occur during ablation as gas is extracted from tissue due to high acoustic pressures and high temperature, forming a gas bubble. Gas bubbles formed during HIFU exposures are highly dynamic and often collapse violently, generating local tissue fragmentation and cavity. Gas bubble formation and pulsation also have the potential to increase localized tissue heating, resulting in asymmetrical lesion formation.

In this study, we investigated biological effects of HIFU during the creation of focal and linear lesions in isolated right atrial (RA) and whole-heart rabbit preparations. Using a combination of optical mapping, optical coherence tomography (OCT), and histology, we evaluated the thermal and nonthermal effects of HIFU on the creation of focal and linear lesions in rabbit cardiac tissue specimens.

Methods

Optical Mapping and Ultrasound Ablation System

Experiments were conducted using the experimental system depicted in Figure 1. This system allows for simultaneous ablation with a custom HIFU system and fluorescence imaging using voltage sensitive dye. Optical mapping was performed with a 100x100 pixel CMOS camera (MiCam Ultima-L, SciMedia USA) focused on the endocardial surface of the preparation. All fluorescence data were acquired at 1000 frames per second. Two 520 nm (±45 nm) light emitting diodes were used for fluorescence excitation. Emission fluorescence was long-passed filtered (>650 nm). Ablation was performed using a 3.5 MHz HIFU transducer (SU-102, Sonics Concepts) connected to a 75W power amplifier (Amplifier Research) and a function generator (Agilent). The HIFU transducer was calibrated in a water tank with a fiber optic hydrophone to measure the peak positive pressure and the spatial-peak pulse-average intensity (ISPPA). The focal distance of the transducer was found to be 57 mm. The 3-dB focal dimension of the HIFU transducer was measured to be 0.6 mm (radial)×7 mm (axial). A pulser-receiver (Olympus Corp.) and an oscilloscope were used to guide the placement of the HIFU focus at the tissue preparation. To ensure precise ablations, the HIFU transducer was attached to a XYZ computer-controlled stage (Zaber Technologies) and controlled with a custom user interface designed in MATLAB (Mathworks). The minimum step size of the XYZ stage is 2 μm.

Tissue Preparations

Two separate tissue preparations were used during HIFU evaluation in this study: Langendorff perfused whole heart preparations (n=6) and isolated RA preparations (n=10). All studies involving the use of animals were approved by the Institutional Animal Studies Care and Use Committee of Washington University in St. Louis. New Zealand white rabbits (n=16, 4–5 months old, 3–4 Kg) were heparinized (1000 U) and anesthetized with pentobarbital (50 mg/kg) intravenously. Following a midsternal incision, the heart was removed and placed onto a Langendorff apparatus, where it was retrogradedly perfused with oxygenated (95% O₂, 5% CO₂) Tyrode solution at 37°C. The heart then was cleaned of fat and pericardial tissue and stained with 50 μL of 15-μM di-4-ANEPPPS (Molecular Probes) over a period of 10 minutes. To create an isolated RA preparation, the intact heart was quickly dissected in a bath of room temperature Tyrode solution to create a preparation containing the right atrial appendage (RAA), the interatrial septum, and a thin strip (approximately 5 mm) of right ventricle (Figure 2). Each preparation was pinned to a custom tissue frame and stretched approximately 3.5 mm (10%) of the unloaded width and 2.5 mm (10%) of the unloaded height. The preparation then was mounted vertically in a custom tissue chamber and superfused at 70 mL/min with perfusate containing 10 μmol/L of the excitation uncoupler B皿bistatin (Tocris Bioscience) to reduce motion artifact during optical mapping experiments. A representative preparation with sinus rhythm OAP and conduction map are shown in Figure 2.

Ablation Protocol

Three ablation protocols were used during experimentation to create (1) point lesions, (2) continuous linear lesions, and (3) continuous linear lesions with a gap in separate preparations. For creation of (1) point lesions, left and right ventricular myocardium was ablated at 973 to 1688 W/cm² for 6 seconds in whole heart preparations (n=6) at 2 locations on the anterior and posterior surface. Ventricular tissue was used to evaluate nontransmural lesion profiles created by HIFU. For evaluation of transmural linear lesions, ablation was performed on isolate RA specimens (n=10). Rabbit atrial tissue was selected for testing due to its thin width (2–3 mm) relative to the focal width (7 mm) of the HIFU transducer. The ratio of tissue thickness to focal width of the transducer ensures that the lesion created would be transmural, an important criteria to achieving conduction block. All linear ablations were performed at 1200W/cm² (7MPa) with a step size of 0.25 mm and ablation duration of 2 seconds to ensure point lesion overlap. Additionally, 5 repeated ablation passes with an axial step size of 0.25 mm were employed to ensure transmural ablation of atrial tissue. To create (2) continuous linear lesions, a linear array of overlapping point lesions was created using the computer controlled system in n=6 preparations. First, a primary linear lesion (5–15 mm) was created from the superior vena cava (SVC) toward the tricuspid annulus. Optical files were recorded every 2.5 mm during ablation to validate lesion progression and completeness of the primary lesion. Next, a secondary linear lesion of 5 to 10 mm was formed from the tricuspid annulus toward the inferior end of the primary lesion. Optical files were recorded after every 1 mm to monitor progression.
of the ablation and connection to the primary lesion. Following completion of the continuous lesion line, tissue was allowed to rest for a minimum of 10 minutes to test sustained conduction block. To evaluate gap size capable of conduction block, (3) linear lesions containing gap sizes of 1 mm, 2 mm, 4 mm, and 6 mm were created in (n=4) RA preparations. For this purpose, a primary linear lesion (5–10 mm) was created from the SVC toward the tricuspid annulus, and optical files were recorded each 2.5 mm during ablation. Next, a secondary linear lesion was formed from the tricuspid annulus toward the inferior end of the primary lesion to leave the appropriate gap size. Tissue was paced at a cycle length (CL) of 250 ms, with a custom platinum bipolar electrode on either side of the lesion line to document conduction through the gap. All HIFU ablation was performed with the power generator set to output powers of 5 to 20W. Accounting for conversion efficiency of electric to acoustic power (~80%), the acoustic power range is approximately 4 to 16W, which is in the range of clinical application.

Optical Coherence Tomography and Histology
Following ventricular ablation of whole heart preparations, tissue preparations were placed in 3.7% formaldehyde diluted in phosphate buffered saline (Sigma-Aldrich) overnight at 4°C. The following day, samples were transferred to a 20% sucrose solution and kept at 4°C for 2 days to dehydrate the tissue. A swept source OCT system (Thor Labs) coupled to a microscope was used to create 3D volumes of specific lesions. The axial and lateral resolution of the system is approximately 9 μm and 25 μm (in water), respectively. Individual OCT images were averaged at most 6 times to decrease noise, depending on the tissue sample at the time of acquisition. OCT data were collected as 512 × 512 × 512 pixel volumes. All volume reconstructions were produced using Volocity software (Perkin Elmer). After OCT imaging, point lesions were extracted from the ventricular walls, sectioned at 16 μm, and stained with Masson’s trichrome stain.

Tetrazolium Staining
Immediately following experimentation on isolated RA preparations, tissue were photographed and stained with triphenyltetrazolium (TTC; Sigma Aldrich) as described. Briefly, tetrazolium powder was diluted in a 2-part phosphate buffer consisting of NaHPO4 (0.1 mol/L) and Na2HPO4 (0.1 mol/L). Phosphate buffer then was combined in a ratio of 77.4%/22.6% (% NaHPO4; % Na2HPO4) to make the final buffer solution. Finally, tetrazolium salts were added at 1% weight/volume (gm/mL). All tissue was incubated in the tetrazolium solution for 10 to 15 minutes at 37°C. Following staining, tissue was photographed again.

Data Analysis
All data analysis was performed using a custom MATLAB GUI (available from efimov.wustl.edu). All optical data were filtered using a 3×3 pixel spatial filter and 2 to 100 Hz FIR bandpass filter and then normalized between 0 and unity. Activation times were defined as the maximum first derivative of the fluorescent signal, dF/dtmax, and activation maps were constructed from the activation times of each pixel on the preparation.

Results

Demonstration of Normal Conduction
Figure 2 demonstrates optical action potentials (OAPs) (Figure 2C) and the conduction pattern (Figure 2B) during sinus rhythm of an isolated RA preparation using our ablation mapping system before the onset of ablation. The activation map and optical signals agree with previously published data for isolated RA preparations from a rabbit. Conduction propagates from the sinoatrial node near the crista terminalis (CT) across the pectinate muscle of the RAA, and finally excites the interatrial septum.

Demonstration of Continuous Linear Ablation
To test our ability to create a continuous line of conduction block, we followed the ablation protocol described previously. Continuous linear conduction block was achieved in 1 (17%) of 6 atrial preparations with a single ablation line (primary and secondary lesion), from the SVC to the tricuspid valve in the RAA. Figure 3 illustrates a typical experiment. Activation maps prior to ablation (Figure 3B) and after ablation (Figure 3C–E) are displayed. Separate panels illustrate the creation of linear lesions of increasing length: 5 mm (Figure 3C), 15 mm (Figure 3D), and 20 mm (Figure 3E). Pink (1) and orange (2) tracings indicate OAPs from opposite sides of the ablation line and illustrate increasing conduction delay with progressive increase in the length of ablation line. Prior to ablation, conduction propagates from the location of the pacing electrode in the RAA, around the inferior end of the CT, and toward the interatrial septum (Figure 3B). After the creation of a 5 mm lesion, conduction in the RAA was altered (Figure 3C). A delay of 15 ms was observed between location 1 (pink) and location 2 (orange). This delay increased to 25 ms as the lesion line was extended from 5 mm to 15 mm (Figure 3D). A clear line of conduction block along the path of HIFU ablation was observed in the activation map.
following connection of primary and secondary lesion lines (Figure 3E). After extending the lesion line through the full length of the preparation, the RAA became electrically isolated from the remainder of the atrial myocardium (Figure 3E). Following isolation, we observed 2 activation rates in the preparation. On the left side of the lesion, the tissue activated with the pacing stimuli at CL = 250 ms. On the right side of the lesion, a spontaneous focus near the location of the sinoatrial node drove activation at a slower rate (CL = 420 ms).

Following a minimum rest period of 10 minutes, 0 (0%) of 6 atrial preparations demonstrated sustained conduction block from a single ablation line. In an attempt to create sustained block, a minimum of 5 additional passes of HIFU energy were applied to the ablation line in axial steps of 0.25 mm. Sustained conduction block was achieved in 1 (17%) of 6 atrial preparations with multiple applications of HIFU energy. When sustained conduction block was unachievable with multiple HIFU applications, multiple lesion lines (average number of lines = 2.0) were created adjacent to the original ablation line. Multiple adjacent lesion lines were successful in creating conduction block in 1 (20%) of 5 atrial preparations. Figure 4 demonstrates an example of a failed electric isolation following both multiple HIFU applications and multiple adjacent lesion lines. Figure 4C depicts normal electric propagation from the pacing electrode (CL = 250 ms) prior to ablation. Following ablation with multiple applications of HIFU and 2 adjacent lesion lines (Figure 4D), conduction occurs through a gap in the lesion line. Post-experimental TTC staining demonstrates a 3 mm-wide transmural region of necrotic tissue (Figure 4B) and a small strip of viable tissue (white arrow) between adjacent lesion lines (Figure 4B). However, the exact location and size of the gap was difficult to determine due to the increased damage caused by additional ablation attempts and multiple lesion lines.

Effects of the Acoustic Radiation Force
As a result of our failure to consistently produce sustained conduction block, we attempted to identify and document potential mechanisms for the failure of HIFU ablation. One potential mechanism of HIFU failure we observed in all of our preparations (16 [100%] of 16) is associated with the acoustic radiation force. To document the phenomenon of acoustic radiation force displacement during our ablation experiments, 3 representative preparations were filmed with a standard video camera from epicardial and transmural views. Figure 5 depicts a transmural view of the tissue before ablation (Figure 5A) and during ablation (Figure 5B). The axial beam profile measured by peak positive pressure and ISPPA are provided for reference in Figures 5C and 5D, respectively. A plastic guard was pinned in place to prevent contact of the HIFU probe with the tissue. Additional ablation attempts were made to create a larger lesion line, and the entire conduction path was ablated in each preparation. In all preparations, the acoustic radiation force displacement was observed, which caused the conduction delay to increase significantly between optical signals from pixel 1 (pink) and pixel 2 (orange). After entire conduction path has been ablated (E), sinus node drives electric excitation on right side of preparation.
front of the tissue for comparative purposes. During HIFU ablation, the tissue is displaced 1 to 3 mm from its original location (Figure 5A) toward the plastic guard (Figure 5B). During this displacement, the target tissue (yellow trace in Figure 5A) is moved from the peak ISPPA of the HIFU beam profile to a lower focal intensity (Figure 5B). Correlation of real time feedback of the computer controlled stage, recorded video, and post-experiment TTC staining indicate gaps in the lesion line at the locations of tissue displacement (indicated by arrows in Figures 5E and 5F).

Effects of Acoustic Cavitation
Another important side effect we identified with HIFU ablation is acoustic cavitation. Audible and visual signs of acoustic cavitation were observed during ablation in all preparations (16 [100%] of 16). Figure 6 demonstrates 2 examples (blue and orange) of acoustic cavitation on the posterior aspect of the heart during ventricular ablations. An audible pop was heard and release of tissue fragments into the perfusate was observed during the creation of both lesions. For the first ablation (blue), 1688 W/cm² was directed toward the left ventricle. Corresponding histological and OCT cross sections through the center of the lesion are displayed in Figures 6B and 6E. While coagulative necrosis was observed on the periphery of the lesion (Figure 6B), a cavity at the lesion center is clearly visible. For the second ablation (orange), acoustic power was reduced to 973 W/cm². Histological sections and OCT sections from the center of the lesion show a circular cavity devoid of tissue, which was obliterated by HIFU (Figures 6C and 6F). Unlike the first lesion (blue), no coagulative necrosis was observed on the periphery of the lesion. This is a particularly severe complication of HIFU, because it irreversibly compromises tissue integrity.

Gap Size for Propagation Through Continuous Lesion Lines
As documented, we observed discontinuous ablation lines and nonsustained conduction block during HIFU ablation with our system. Hence, we attempted to document the minimum gap size in a lesion line produced by HIFU that could sustain conduction. Figure 7 demonstrates optical mapping and histological results during the creation of a 2 mm gap in a single atrial preparation. Prior to ablation (Figure 7C), conduction was observed to propagate from the pacing electrode near the SVC and CT across the RAA, around the inferior portion of the CT, and toward the inferior vena cava. Figure 7D depicts conduction through a 6 mm gap. Following ablation, conduction moves through the gap and bifurcates into 2 pathways, (1) a superior path toward the SVC, and (2) an inferior path toward the atrioventricular groove. A similar conduction pattern was observed as gap size was decreased to 4 mm (Figure 7E) and 2 mm (Figure 7F). Following experimentation, the final gap size and lesion lines in the tissue were examined (Figure 7G). Using a scalpel, the tissue was divided along with the lesion line to expose a cross sectional surface. The gap and ablation lines can be identified easily as red viable tissue and white ablated tissue, respectively. The final gap size in the tissue cross section was measured at 1.5 mm. In other experiments, conduction through gap sizes as small as 0.5 mm and 1 mm were tested. However, due to the distributed nature of the HIFU beam profile, as well as other factors discussed previously, documentation of creation of smaller gaps proved difficult with our specific transducer.

Discussion
To date, the majority of cardiac HIFU research has focused on the thermal effect of HIFU. Thermal dose is a critical component of ablation success, and prior research has been crucial in understanding the thermal capabilities of HIFU. Much like other ablation technologies, however, thermal deposition is not the only factor that occurs during HIFU application to tissue. In this study, we demonstrate 3 contributing factors to HIFU ablation: acoustic radiation force, acoustic cavitation, and discontinuous linear lesions.

Besides the primary thermal effect of HIFU, acoustic radiation force associated with HIFU application can displace tissue away from the HIFU focal zone, shifting the location of the intended ablation site away from the HIFU focus. During
Acoustic radiation force.

A. Side profile of right atrial preparation before high intensity focused ultrasound (HIFU) application. Yellow trace indicates profile of tissue surface. Black dashed trace indicates axial beam profile relative to tissue surface. B. Side profile of right atrial preparation during HIFU application. Red trace indicates displaced profile of tissue surface. Red arrows indicate direction of HIFU application. C. Peak positive pressure axial beam profile as a function of position from transducer face. D. Spatial-peak pulse-average intensity axial beam profile as a function of position from transducer face. E. Right atrial preparation. Red line indicates ablation line. F. Triphenyltetrazolium staining post ablation. Arrows indicate gaps in ablation line.

In our experimental study, tissue displacement of 1 to 3 mm was noted in all atrial (n=10) and ventricular (n=6) preparations. Displacement by acoustic radiation force was highly dependent on tissue properties. Thinner, more flexible tissue displayed greater displacement than thicker tissues. Depending on the amount of displacement in the focal zone, the targeted tissue site may not reach the necessary temperature during exposure to achieve irreversible cell death, and gaps in lesion lines may occur (as shown in Figure 4). Moreover, tissue could become temporarily stunned, but not fully ablated, allowing a conduction pathway to reestablish itself after a recovery period. In addition, unintended tissue sites can be inadvertently moved into the HIFU focus, causing unwanted damage. In recent clinical evaluations of St. Jude’s Epicor HIFU system, researchers reported temporal damage to the phrenic nerve and collateral damage to the esophagus during epicardial HIFU application.9,10 One explanation for these findings might be acoustic radiation force pushing the phrenic nerve into a focal zone conducive to nerve damage.

Another important and potentially dangerous phenomenon occurring during HIFU application is acoustic cavitation or gas bubble activity. Acoustic cavitation occurs because of the rapid creation and collapse of gas bubbles within tissue, which could result from high acoustic pressure or high temperature induced by HIFU.20 Much like “steam pops” produced during radiofrequency ablation, acoustic cavitation poses a substantial risk to patients. Cavitation could result in embolic events, tamponade, or cardiac perforation. Despite HIFU being used for many clinical applications, cavitation thresholds and effects are poorly understood.20 Researchers have shown that cavitation is dependent on various tissue and transducer parameters, such as convective cooling from nearby blood vessels, applied acoustic frequency, and tissue heterogeneities.20,22,23 In the current study, we present 2 examples of acoustic cavitation producing cavities in myocardium (Figure 6). Additionally, we also observed several audible “pops” during the creation of linear lesions in all experiments, an observation not often mentioned by other researchers. One reason for missing this phenomenon in previous studies could be related to differences in the experimental design. We use oxygenated Tyrode solution to provide a physiological environment for the heart, while other experimental evaluations of HIFU have been carried out in degassed saline.2,3,24 We feel Tyrode solution more accurately replicates in vivo gas conditions, as well as decreases the risk of tissue ischemia. Increased gas levels in solution could lead to increased cavitation risk. Again, this might explain some of the reported side effects with the Epicor system on human subjects.9

Continuous, transmural lesion lines are vital to the success of ablation therapies.25,26 We attempted to investigate ablation success and importance of gap size to conduction block. Currently, controversy exists in reported gap sizes necessary for sustained acute conduction block. Melby et al26 reports successful conduction in 93% of gaps between 1 to 3 mm, and conduction block for all gaps less than 1 mm. More recently, Ranjan et al25 described median gap length of 4.15 mm in canine ventricles as sufficient for conduction block. Our system provides a unique opportunity to create precise lesion lines and gaps in cardiac tissue. Using this system, we briefly evaluated the smallest viable gap that allows conduction. Similar to results from Melby et al,26 we observed conduction through gaps of 1 to 3 mm in our experiments. These small gaps underscore the importance of controlling the effects of acoustic radiation force and cavitation. Disturbances that move tissue out of the HIFU focus or create irregular tissue damage can produce gaps on the order of 1 mm that decrease ablation success and may increase the need for reablation procedures. Lesion discontinuity is not, however, completely based on nonthermal effects. Incomplete lesion lines easily can result from inconsistent thermal deposition due to the distributed nature of the HIFU beam profile.

Future HIFU research should focus on how to mitigate the effects of acoustic pressure and acoustic cavitation while promoting spatio-temporal thermal deposition. One way this might be achieved is through simultaneous (or real-time) monitoring of ablation. Dual element transducers might be able to use a combination of diagnostic ultrasound and therapeutic ultrasound to ablate tissue and monitor lesion
progress and tissue displacement. This approach would allow physicians to use the novel aspects of HIFU, while ensuring ablation success.

Limitations
We would like to acknowledge a few important limitations to our study. First, HIFU ablation was performed in an in vitro setting on atrial tissue mechanically arrested using Blebbistatin. To compensate reduction of stiffness caused by Blebbistatin, atrial preparations were stretched as specified. In vivo ablation on a beating heart with changing tissue tensions may potentially result in different HIFU tissue interactions. Thus, reported mechanisms of failure observed in vitro may not entirely represent in vivo ablation. Additionally, our isolated

Figure 6. Acoustic cavitation. A Posterior aspect of rabbit heart used for ablation. Blue and orange circles indicate location of lesions produced with high intensity focused ultrasound. Blue lesion was created using 1688 W/cm² of acoustic power and the orange lesion was created using 973 W/cm² of acoustic power. B Histological cross section through center of blue lesion. C Histological cross section through center of orange lesion. D Zoomed in image of posterior field of view. E Optical coherence tomography (OCT) volume of blue lesion. Exposed face represents cross section corresponding to histology. F OCT volume of orange lesion. Exposed face represents cross section corresponding to histology. RV indicates right ventricle; LV, left ventricle.

Figure 7. Conduction through gap. A Endocardial view of isolated right atrial preparation with important structures labeled. Red dashed line indicates ablation line. Yellow outline indicates optical field of view. Black square pulse represents pacing location. B Endocardial view of right atrial preparation post triphenyltetrazolium staining. White arrow indicates ablation line. C Activation map before ablation. D Activation map after creation of 6 mm gap. E Activation map after creation of 4 mm gap. F Activation map after creation of 2 mm gap. G Cross section through center of lesion. White outlines indicate ablated tissue surface exposed with scalpel. Upper outline (1) indicates upper half of lesion line, and lower outline (2) represents lower half of lesion line.
preparations are unlikely to replicate the effect of tissue surrounding the heart. The altered biomechanical environment may modulate the effects of acoustic cavitation and acoustic radiation force. Nevertheless, the complications observed in this study using simplified preparations also have been observed in more complex clinical evaluations of HIFU.

Conclusion

Three mechanisms were identified to interfere with the creation of linear conduction block during HIFU ablation: acoustic radiation force, cavitation, and discontinuity in linear lesions. If HIFU is to become a feasible option for cardiac ablation, the various mechanisms of tissue damage induced by HIFU need to be understood properly. Moreover, strategies need to be developed to mitigate the effects of acoustic radiation force and acoustic cavitation while promoting thermal deposition.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

High intensity focused ultrasound (HIFU) offers a great opportunity to develop effective strategies for noninvasive or minimally invasive treatment of atrial fibrillation and other arrhythmias. Despite its promises, current HIFU technology has failed to demonstrate high standards of safety and efficacy. This manuscript identifies 3 potential mechanisms that may be responsible for the failure of current HIFU technology: acoustic cavitation, acoustic radiation force, and discontinuous linear lesions. Improving our understanding of these mechanisms and their role in the creation of transmural lesions will facilitate the development of new HIFU technologies that would improve patient outcomes. Specifically, this research underscores the critical need for real time feedback to monitor thermal deposition in 3D space and acoustic pressure.
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