Extracardiac Ablation of the Canine Atrioventricular Junction by Use of High-Intensity Focused Ultrasound

S. Adam Strickberger, MD; Takashi Tokano, MD; Jan-Ulco A. Kluijstra, MS; Fred Morady, MD; Charles Cain, PhD

Background—High-intensity focused ultrasound has been applied to internal organs from outside the body to ablate tissue. No published study has assessed the feasibility of ablating cardiac tissue within the beating heart by use of this type of therapeutic ultrasound. The purpose of this study was to determine whether high-intensity focused ultrasound can be used to ablate the atrioventricular (AV) junction within the beating heart.

Methods and Results—Ten dogs were anesthetized and underwent a thoracotomy. The heart was covered with a polyvinyl chloride membrane. The thorax above the membrane was perfused with degassed water, which functioned as a coupling medium for the ultrasound. A 7.0-MHz diagnostic ultrasound probe was affixed to a spherically focused 1.4-MHz high-intensity focused ultrasound transducer with a 1.1×8.3-mm focal zone 63.5 mm from the ablation transducer. The diagnostic ultrasound probe was calibrated such that the location of the focal zone of the ablation transducer was identifiable on the 2-dimensional ultrasound image. Target sites were identified with the diagnostic ultrasound. The maximum ultrasound intensity for ablation (2.8 kW/cm²) was delivered to the AV junction only during electrical diastole and for a total of 30 seconds. Complete AV block was achieved in each of the 10 dogs with 6.5±5.6 (range, 3 to 21) 30-second applications of therapeutic ultrasound. Gross inspection showed that the mean lesion volume was 124±143 mm³, with a depth of 6.7±3.6 mm, a length of 5.7±2.5 mm, and a width of 4.7±1.8 mm. Four hours after the dogs were killed, histopathological study demonstrated a well-demarcated area of necrosis and early inflammation.

Conclusions—High-intensity focused ultrasound produces well-demarcated lesions and appears to be a feasible energy source to create complete AV block within the beating heart without damaging the overlying or underlying cardiac tissue. This energy source may allow for a noninvasive approach to ablation of cardiac arrhythmias. (Circulation. 1999;100:203-208.)

Key Words: ablation ■ atrioventricular node ■ arrhythmias

H igh-intensity focused ultrasound has been used to ablate deep tumors.1–5 This type of therapeutic ultrasound energy offers the advantage of being applied from outside the body to create a lesion of essentially any size and geometry.6 High-intensity ultrasound can also be focused up to 15 cm within the body without heating or damaging the intervening tissue.6 Therapeutic ultrasound has been used to treat a variety of conditions.1,2,4,5,7–14 However, the use of extracardiac ultrasound to ablate functioning myocardium has not been reported. The purpose of this study was to determine whether extracorporeal focused ultrasound can be used to create atrioventricular (AV) block within the beating canine heart.

Methods

Experimental Preparation

The University of Michigan Committee on the Use and Care of Animals approved the protocol. Ten mongrel dogs of either sex (37±7 kg; range, 27 to 50 kg) were used for this study. The dogs were anesthetized with sodium pentobarbital 10 to 30 mg/kg IV and then underwent endotracheal intubation and mechanical ventilation. General anesthesia was maintained with supplemental doses of sodium pentobarbital. Arterial blood gases were evaluated periodically, and ventilation was adjusted to maintain the arterial pH at 7.35 to 7.45. A hemostatic sheath was inserted into a jugular vein, and another was inserted into a carotid artery to allow for arterial blood pressure monitoring. A sternotomy was performed, and a retractor was positioned to expose the pericardium (Figure 1). A polyvinyl chloride membrane was positioned over the heart and lungs. To exclude air bubbles and to improve the acoustic coupling, saline was applied to the surface of the heart and the underside of the polyvinyl chloride membrane. The thoracic cavity was perfused at 600 mL/min with degassed water above the membrane. The degassed water functioned as an ultrasound coupling medium. The ultrasound ablation system was placed inside the thorax in the degassed water and positioned over the AV groove. The surface ECG and the arterial blood pressure were displayed and recorded on a multichannel recorder (Electronics for Medicine VR 16).

Combined Diagnostic/Ablation Ultrasound System

The diagnostic ultrasound component of the combined ultrasound system used a conventional 2-dimensional (2D) ultrasound machine...
Ablation Protocol

The 2D ultrasound images were used to identify the AV junction (Figure 2). All target sites were identified directly from the 2D ultrasound image. The calibration mark indicating the focal zone of the ablation transducer was displayed on the imaging monitor throughout the experiment and defined the location of the focal point of the ablation transducer within the 2D ultrasound image (Figure 2). This allowed the identification of ablation targets by use of the ultrasound image.

Microscopic Evaluation

Pathological examination was completed in 4 animals. Lesions from 3 animals were sent for microscopic evaluation immediately after euthanasia. One additional animal was killed 4 hours after complete AV block was created to allow evolution of the lesion. Representative blocks of tissue encompassing the lesion and including the epicardium and the surrounding myocardium were identified by visual inspection. These blocks were fixed in 10% formalin and embedded in paraffin. Sections were subsequently stained with hematoxylin and eosin.

Results

Main Findings

Complete AV block was created in each of the 10 animals with 30-second applications of ablative ultrasound at a mean of 6.5±5.6 target sites (range, 3 to 21; Table; Figures 2 and 3). Junctional ectopy preceded complete AV block in each animal. The mean escape rate was 61.4±12.8 bpm (range, 40 to 80 bpm), with a QRS duration of 105±13 ms. The mean lesion volume was 124±143 mm³, with a depth of 6.7±3.6 mm (range, 1 to 15 mm), a length of 5.7±2.5 mm (range, 1 to 9 mm), and a width of 4.7±1.8 mm (range, 3 to 8). Lesion appearance was accompanied by the formation of an echo-dense area at the targeted focal zone in each animal (Figure 2). Three animals developed ventricular fibrillation during an application of ablative ultrasound energy. Sinus rhythm was restored with electrical defibrillation in each instance.

Gross and Microscopic Pathology

By gross inspection, each lesion was well demarcated and surrounded by normal adjacent tissue (Figure 3). The myocardium between the ultrasound ablation transducer and the lesion was unaffected (Figure 3). Anatomically, the location of lesions always was consistent with the target sites identified by 2D ultrasound.

Pathological examination was completed in 4 animals. Microscopic examination of tissue from the 3 animals killed immediately after complete heart block was achieved showed a well-demarcated area of very acute inflammation. The adjacent tissue was histologically normal. Microscopic examination of tissue from the 1 animal killed at 4 hours demonstrated a well-demarcated lesion (Figure 4). The myocardium immediately adjacent to the lesion, including the tissue between the lesion and the ablation ultrasound transducer, was histologically normal. Within the lesion, necrosis was clearly evident, with increased eosinophilia of myocyte cy-
Discussion

Main Findings
This study demonstrates that extracardiac ablation of the AV junction can be achieved in the beating heart by use of high-intensity focused ultrasound. Applications of ablative ultrasound energy produced well-demarcated lesions that demonstrated thermal coagulation. Lesion formation was consistently associated with the development of a small echo-dense area on the 2D ultrasound image. The myocardium adjacent to the lesions, including the tissue between the lesion and the ablation ultrasound transducer, was unaffected by the ablative ultrasound energy.

Pathology and Mechanism of Lesion Formation
The lesions created in this study with high-intensity focused ultrasound were well demarcated. Similar lesions have been observed when high-intensity focused ultrasound was used to create lesions in noncardiac tissue. The pathology of the acute lesions noted in the present study is similar to that of the well-demarcated lesions created with radiofrequency energy. This type of well-demarcated lesion is not believed to be associated with a risk of proarrhythmia. However, the effect of time on cardiac lesions created with high-intensity focused ultrasound energy has not been evaluated.

Imaging of Ablation Targets and Lesions
Intracardiac ultrasound imaging has been used to direct applications of radiofrequency energy and to observe the development of lesions generated by radiofrequency catheter ablation. In animals subjected to radiofrequency catheter ablation, the lesion size noted with intracardiac ultrasound correlates well with the lesion size observed postmortem. In the present study, diagnostic ultrasound was used to select ablation target sites and to monitor

Figure 2. Images of heart obtained with diagnostic ultrasound before (A) and after (B) ablation of AV junction. Diagnostic ultrasound image was calibrated such that focal point of ablation ultrasound transducer is indicated with X. A, X is positioned at crux of interventricular septum and indicates target. After a 30-s application of high-intensity focused ultrasound, complete AV block developed (B). An echo-dense lesion is visible at target. Surface ECG lead associated with ultrasound image is shown at bottom of each figure. AO indicates aorta; LA, left atrium; RA, right atrium; RV, right ventricle; and TV, tricuspid valve.
lesion formation. Lesion formation was associated with the development of an echo density at the target site. These preliminary data suggest that combining diagnostic ultrasound imaging with ultrasound ablation may provide a technique for identifying target sites and for recognizing when an energy application has resulted in lesion formation.

Comparison With Transcatheter Ultrasound Ablation

Ultrasound cardiac ablation has been performed in dogs with a 7F catheter.\textsuperscript{21,22} The lesion depth and volume were similar to those created with radiofrequency catheter ablation.\textsuperscript{18,21,22} Catheter-based ultrasound ablation requires $10 \text{ MHz}$ to produce adequate tissue absorption. Approximately $10 \text{ W}$ of acoustic power is needed; there is direct tissue contact, and lesion depth is $\approx 8 \text{ to } 10 \text{ mm}$.\textsuperscript{21,22} In the present study, target sites for ablation were selected with conventional, noninvasive, 2D ultrasound, and tissue contact was not required. The high-intensity ultrasound used $120 \text{ W}$ of total acoustic power that was focused and used to ablate tissue at a distance of $6.3 \text{ cm}$ from the transducer without damaging the intervening tissue. High-intensity focused ultrasound has been used in an in vitro system to create lesions of various sizes and shapes, in a variety of locations, within the complex anatomy of the canine heart.\textsuperscript{23} A phased-array therapeutic ultrasound system composed of tens or hundreds of ultrasound elements may be used to create lesions at specific target depths up to $15 \text{ cm}$, without significant heating of the intervening tissue.\textsuperscript{6} Phased-array systems may be suitable for noninvasive cardiac ablation because of the ability to control for the position of the target site by switching between different beam patterns at electronic speed, to correct for aberrations due to complex inhomogeneous intervening tissue, such as the ribs and lungs, and the ability to change the effective aperture dimensions during treatment by adjusting the driving signals.\textsuperscript{6,24,25}

Previous Studies Using High-Intensity Ultrasound

Previous investigators have evaluated noninvasive high-intensity focused ultrasound in vivo and in vitro for the treatment of a variety of disorders.\textsuperscript{1,2,4,5,9,11,14,26} Catheter-based ultrasound ablation has been used to dissolve clots in patients with acute myocardial infarctions, and externally delivered ultrasound has proved effective for recanalizing thrombosed iliofemoral arteries in rabbits.\textsuperscript{26,27} The present study is the first to report that high-intensity ultrasound energy can be focused from outside the beating heart to a desired location within this organ without damage to intervening tissue.

Technological Limitations of Ultrasound Ablation

A spherically focused single-element ultrasound ablation system, as used in the present study, cannot be used to ablate cardiac tissue through a closed chest. However, modeling

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<th>Animal</th>
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Mean $6.5 \pm 5.6$ $5.7 \pm 2.5$ $6.7 \pm 3.6$ $4.7 \pm 1.8$ $124 \pm 143$

Application indicates number of 30-s applications of high-intensity focused ultrasound required to achieve complete AV block.
studies of a human chest phantom demonstrated the feasibility of using a phased-array ultrasound system for precise beam formation within the thorax and around the ribs. In addition, many parameters, such as frequency, the ratio between the aperture size and focal depth, and duration of energy application, can affect lesion size and volume. These factors need to be more completely understood to optimize lesion formation. In addition, lesion volume varied between animals. Differences in biological factors may have contributed to this variation, or perhaps the variable lesion size resulted from applications that did not form lesions, from overlap of successive target sites, or because the focal zone was small.

Conclusions and Implications
These results demonstrate that extracardiac application of ablative ultrasound energy gated to the cardiac cycle and guided by diagnostic 2D ultrasound can be accurately aimed at the AV junction and can create complete AV block in the beating canine heart without damaging adjacent tissue. The lesions are well-demarcated and consistent with thermal necrosis. This technology may form the basis of extracorporeal application of an ablative energy that can create controlled lesions of various sizes and shapes. Theoretically, a combined diagnostic and therapeutic phased-array ultrasound system may allow for noninvasive ablation of cardiac arrhythmias.

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References


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