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

S. Adam Strickberger, MD; Takashi Tokano, MD; Jan-Ulco A. Kluiwstra, 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 1.1×3.3-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
The ablation ultrasound transducer was positioned 63.5 mm from target (X) with a mechanical 3-dimensional positioning system.

The calibration mark indicating the focal zone of the ablation transducer was positioned 63.5 mm from target (X) with a mechanical 3-dimensional positioning system.

Figure 1. Schematic of experimental apparatus. A polyvinyl chloride membrane covers heart (as illustrated) and lungs (not shown). Degassed water flows in and out of thoracic cavity at 600 mL/min. Combined diagnostic/ablation ultrasound fixture is placed into degassed saline. Ultrasound ablation transducer was positioned 63.5 mm from target (X) with a mechanical 3-dimensional positioning system.

(Diasomics VST Master Series, Diasomics/Vingmed Ultrasound Inc) with a 7.0-MHz probe that was affixed to the ablation ultrasound transducer (Figure 1). The ablation ultrasound transducer was a spherically focused single piezoelectric element (Etolon). The radius of curvature was 63.5 mm, and the focal point was 63.5 mm from the transducer. The operating frequency of the transducer was 1.44 MHz, and the focal zone (−6 dB) was 1.1 mm wide and 8.3 mm long. In all experiments, the continuous-wave spatial peak temporal average intensity was 2.8 kW/cm². This is orders of magnitude greater than that associated with diagnostic and transcather ablation ultrasound. The spherically focused ablation transducer exposed tissue to high-intensity focused ultrasound energy in a cone shape. The input impedance of the ablation transducer was electrically matched to the 50-Ω output impedance from the linear amplifier. The high-intensity focused ultrasound transducer was driven by a function generator (model 23, Wavetek) and a high-power amplifier (300-W maximum; AP 400B, ENI). The high-power amplifier and the function generator produced a gated sinusoidal waveform at 1.44 MHz. The ablation ultrasound transducer was positioned 63.5 mm from the target by use of a 3-axis mechanical manipulator.

Calibration of the Ablation Ultrasound Transducer to the Ultrasound Image

A 63.5-mm-long pointer, a length identical to the distance to the focal point of the ablation ultrasound transducer, was attached to the ablation ultrasound transducer. The combined ablation and imaging fixture was placed in a degassed water bath. The location of the tip of the pointer, relative to the diagnostic ultrasound image, was noted on the ultrasound imaging monitor. This location 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.

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 positioned at the summit of the interventricular septum. A computer interface (Gateway 2000) was used to control the duration and timing of each energy application. Because of cardiac motion and the desire to create well-defined lesions at the AV junction, applications of ablative energy were gated to the QRS complex and delivered only during electrical diastole, as defined by the average preablation heart rate. Mechanical ventilation and diagnostic ultrasound imaging were continued during applications of ablative energy. The ablation ultrasound energy was applied for a total of 30 seconds. The total number of applications per target site (119.7±7.7) required to achieve a total application duration of 30 seconds depended on the sinus cycle length (384±36 ms). The initial target site was selected at the summit of the interventricular septum. If complete AV block did not develop with a 30-second application of ablative ultrasound energy, a new target slightly below or adjacent to the previous target site was selected by use of the 2D ultrasound image, and an additional 30-second application of energy was delivered. This was repeated until complete AV block was induced.

After completion of the experimental protocol, the animals were euthanized by an intravenous injection of supersaturated potassium chloride. The heart was removed, and the lesion in the AV junction was localized grossly. The 3 dimensions of the lesion were measured, and the lesion volume was calculated according to the following equation, which describes an ellipsoid: Ablation Protocol

Lesion volume = (4/3)π×length/2×depth/2×width/2.

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
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. The lesion depth and volume were similar to those created with radiofrequency catheter ablation. Catheter-based ultrasound ablation requires ≥10 MHz to produce adequate tissue absorption. Approximately 1 W of acoustic power is needed; there is direct tissue contact, and lesion depth is ~8 to 10 mm. 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 W of total acoustic power that was focused and used to ablate tissue at a distance of 6.3 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. 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 cm, without significant heating of the intervening tissue. 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.

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. 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. 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

<table>
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Mean: 6.5 ± 5.6; 5.7 ± 2.5; 6.7 ± 3.6; 4.7 ± 1.8; 124 ± 143

Application indicates number of 30-s applications of high-intensity focused ultrasound required to achieve complete AV block.

**Figure 3.** Gross pathology of a lesion associated with complete AV block. In this figure, aortic valve (AoV) is labeled, and left main and right coronary artery ostia are visible. Left ventricular free wall (far right of figure) was disarticulated from interventricular septum (Septum). Septum was then cut longitudinally to expose septum and lesion (inside dashed circles). AV septum is immediately above lesion. Right atrium is noted to left of AV septum. To left of interventricular septum, and not shown, is right ventricle. Note that lesion is well demarcated and that surrounding myocardium appears normal.
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.

Acknowledgments
Dr Tokano was supported in part by Research Fellowship Award 17F967 from the American Heart Association of Michigan. The authors greatly appreciate the assistance of Gerald D. Abrams, MD, of the Department of Pathology at the University of Michigan.

References

Figure 4. Hematoxylin-eosin-stained tissue section obtained from a dog that was euthanized 4 hours after complete AV block was created with high-intensity focused ultrasound. Necrosed tissue is well demarcated from normal tissue at bottom left of figure. Within lesion, early necrotic changes, including increased cytoplasmic eosinophilia, prominent contraction bands, and early leukocyte infiltration, are present.


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Circulation. 1999;100:203-208
doi: 10.1161/01.CIR.100.2.203

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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