High Intensity Focused Ultrasound Effect on Cardiac Tissues:

Potential for Clinical Application

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High intensity focused ultrasound (HIFU) is an evolving technology with potential therapeutic applications. Utilizing frequencies of 500 kHz to 10 MHz, HIFU causes localized hyperthermia at predictable depths without injuring intervening tissue. Applications in neurosurgery, urology, oncology and, more recently, cardiology for selective cardiac conduction tissue ablation have been promising. A 'noninvasive' technique for causing localized tissue damage to relieve hemodynamic and life-threatening obstruction in patients with congenital cardiac anomalies could replace more invasive procedures. We, therefore, investigated the ability of HIFU to create lesions in mammalian cardiac tissues ex vivo. Porcine valve leaflet, canine pericardium, human newborn atrial septum, and right atrial appendage were studied. Specimens were mounted and immersed in a water bath at room temperature. Using a 1-MHz phased array transducer, ultrasound energy was applied with an acoustic intensity of 1630 W/cm^2 or 2547 W/cm^2 until a visible defect was created (duration 3 to 25 sec). Macroscopic and microscopic examination demonstrated precise defects ranging from 3 to 4 mm in diameter. No damage was identified to the surrounding tissues. Our study concluded that HIFU can create precise defects in different cardiac tissue without damage to the surrounding tissue. Further investigation is needed to assess potential clinical uses of this technology. (ECHOCARDIOGRAPHY, Volume 17, No. 6, Part 1, August 2000)

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High intensity focused ultrasound (HIFU) is an evolving technology with several potential applications. Utilizing frequencies of 500 kHz to 10 MHz, HIFU can cause controlled, localized tissue damage through a combination of thermal energy (tissue absorption of acoustic energy) and mechanical energy (oscillation and collapse of gas bubbles or microcavitation).[1,2]

In 1954 Fry et al.[3] introduced HIFU to disrupt tissue in the central nervous system. Since then, lesions have been created in murine and canine kidney and liver,[4,5] rabbit brain and kidney,[2,6] canine prostate,[7] and human prostate, testes, and kidney.[7,8] Light and electron microscopy have demonstrated a sharp boundary between the damaged tissue and the surrounding, unaffected tissue.[5,8] Foster et al.[9] have demonstrated similar results in living organisms using transrectal probes in canines and humans. Other investigators have documented the use of HIFU to create thrombosis or to enhance thrombolysis.[10-17] More recently, studies using intravascular HIFU for cardiac conduction tissue ablation have been promising.[18-20]

Interventional cardiac catheterization is often used to create or dilate openings or passages within the heart. Although advances in these techniques have improved their safety and efficacy, they are not risk free. Vitiello et al.[21] recently reported an overall complication rate of 20% in pediatric patients undergoing interventional cardiac catheterization; mortality was 0.14%. A less invasive technique for creating localized cardiac defects could potentially reduce the need for and the risk of these invasive procedures. The purpose of this study

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was to investigate the ability of HIFU to create lesions in mammalian cardiac tissues ex vivo.

Methods

A piezocomposite, spherical shape, 64-element, one-dimensional array transducer (Imasonic, France) was used. This device was designed for the purposes of producing lesions in various tissues. The transducer has a rectangular aperture of 120 mm by 50 mm with a radius of curvature of 100 mm. All of the elements were pulse driven in phase, resulting in a fixed focus at the geometric center with an elliptical cross section in both the lateral and longitudinal directions. The major and minor of the ellipse in the lateral direction are 2.2 mm and 1 mm, respectively, and in the longitudinal direction are 12 mm and 1 mm, respectively. Defects created in samples positioned perpendicular to the ultrasound beam corresponded to the lateral cross section of the beam. A commercially available Pentium computer controlled the amplitude (15 selectable values at 1 MHz) and phase ($\pi/15$ resolution at 1 MHz) for each of the array elements which were capable of producing focal intensity levels up to 5400 W/cm^2 at 1 MHz with surface intensities up to 10 W/cm^2 (intensity gain of nearly 540). These intensity levels produce thermal coagulation of most tissues and, under certain conditions, mechanical tissue damage. To maximize thermal effects, we operated at peak focal intensity levels of 1630 W/cm^2 or 2547 W/cm^2.

Tissue samples included porcine pulmonary valve ($n=1$), canine pericardium ($n=1$), human newborn atrial septum ($n=3$), and human newborn right atrial appendage ($n=1$). The human tissues were obtained from infants with hypoplastic left heart syndrome undergoing a modified Norwood procedure and atrial septectomy. Unfixed specimens were stored at $-20°$ until the day of study and then sutured with 6.0 Prolene (Ethicon Inc., Somersville, NJ, USA) to the edges of a hole in a Gore-Tex® patch (W.L. Gore and Associates Inc., Elkton, MD, USA). The mounted tissue was then suspended in a plexiglass ring. The whole assembly was immersed in a room temperature, degassed[22] water bath at the transducer focal point (Fig. 1).

Ultrasound was empirically applied with an acoustic intensity at the focus of either 1630 W/cm^2 or 2547 W/cm^2 for 3-25 seconds and repeated until a lesion became macroscopically visible. Macroscopic examination and photography were performed. The specimens were then fixed in 10% buffered formalin, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin for microscopic examination.

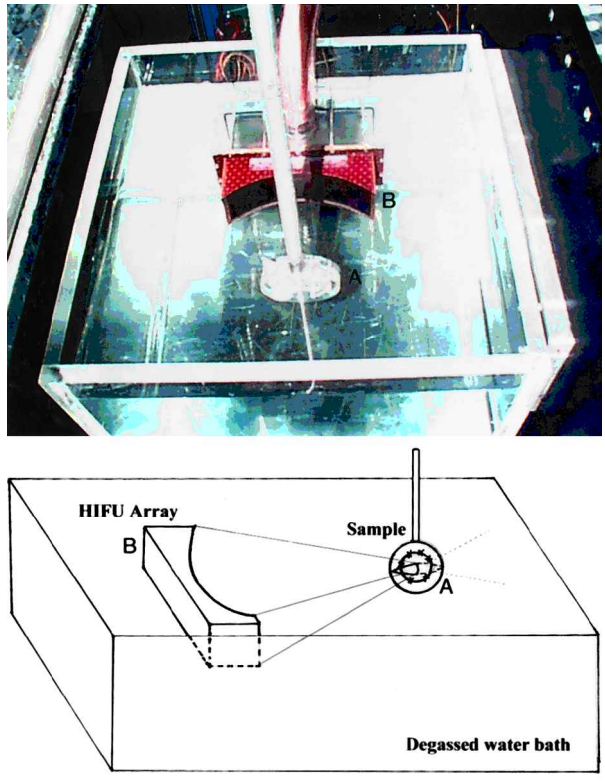

Figure 1. *Experimental setup. Specimen* **A.** *is suspended in the center of a plexiglass ring positioned perpendicular to the phased array transducer at its focal zone* **B**. *The specimen and transducer are submerged in a degassed water bath.*

Results

Lesions were produced in all tissues studied for a total of nine lesions. The porcine valve leaflet (Fig. 2A), newborn right atrial appendage, and two samples of newborn atrial septum (Fig. 2B) had one lesion each. One sample of canine pericardium had three lesions, and one human newborn atrial septum had two lesions. Intensity of ultrasound energy and duration per application for each lesion are summarized in Table I. A median of two applications was required to create each lesion (range 1-5) applied for a duration of 3-25 seconds (median 10 sec). Tissues requiring more than one application were noted too thin in the focal zone between applications. Tissues sutured under less

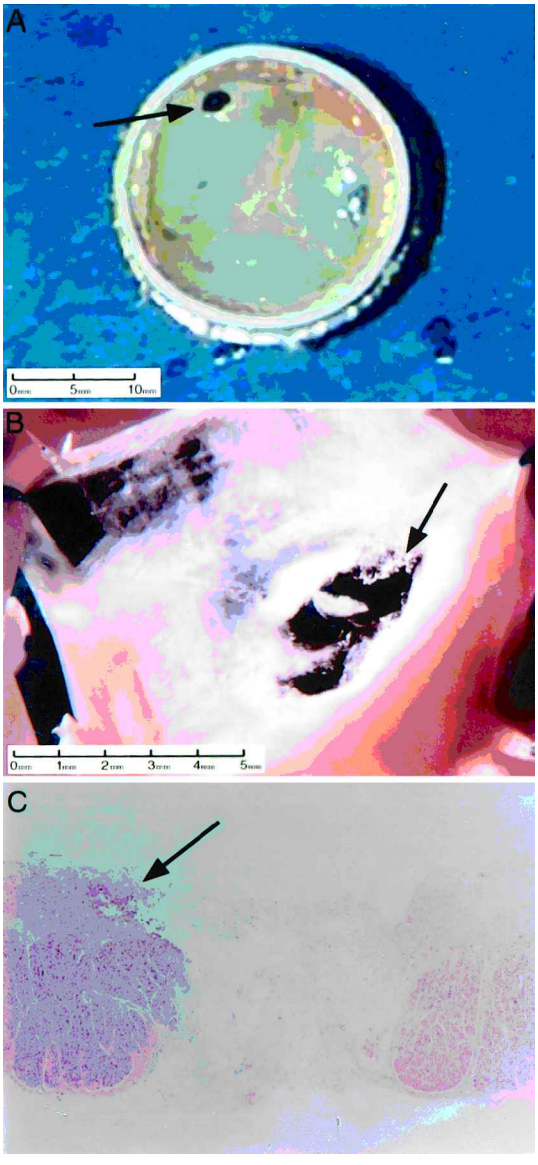

Figure 2. *Lesions created using HIFU.* **A.** *Porcine pulmonary valve with lesion in the lateral portion of one leaflet (arrow).* **B.** *Atrial septum after application of HIFU.* **C.** *Microscopic section of atrial septum taken near the edge of the defect (40×) demonstrating central dissolution of tissue with a narrow zone of focally damaged tissue (arrow) surrounded by unaffected tissue.*

tension ballooned during HIFU application. Some applications resulted in a central band of tissue, which broke upon removal from the water bath. All of the lesions were well circumscribed, measuring 3-4 mm in diameter. The shape of the lesions was elliptical, circular, or nonuniform. Microscopic examination showed a central area of complete tissue dissolution and a narrow surrounding rim with varying degrees of damage. The tissue outside of this rim appeared unaffected (Fig. 2C).

Discussion

This study demonstrates that the technology of HIFU can accurately create defects in mammalian cardiac tissues under nonphysiological conditions. Many issues need to be addressed before clinical application of this technique would be feasible. Studies done at body temperature in a medium with properties similar to blood will affect the temperatures required and created by HIFU. Ambient temperatures will also likely affect the temperature changes and effects on surrounding tissues. By study design, there was no measurement of temperature changes during application. Therefore, the relative

TABLE I.

Summary of High Intensity Ultrasound Applications to Create Cardiac Lesions

Defect	Tissue	Ultrasound Energy Applied (Watts/cm^2)	Duration of Application (sec)
1	Porcine	2547	5
	pulmonary	2547	10
	valve	2547	10
2	Canine	1630	3
	pericardium	1630	3
		1630	4
3	Canine	1630	10
	pericardium	2547	10
4	Canine	2547	10
	pericardium		
5	Newborn right	2547	12
	atrial		
	appendage		
6	Newborn	2547	25
	atrial	1630	25
	septum		
7	Newborn	1630	5
	atrial	1630	5
	septum	1630	5
		1630	5
8	Newborn	1630	5
	atrial	2547	5
	septum	1630	10
		1630	10
		1630	10
9	Newborn	1630	15
	atrial		
	septum		
Median			10

contribution of thermal and mechanical energy are not known. Determination of the optimal transducer geometry, operating frequency, intensity level, and exposure time is dependent on knowledge of the exact mechanism of cardiac tissue damage. Consequently, future studies delineating the mechanism of defect formation are imperative to designing a transducer for clinical application.

To deliver cardiac treatment 'noninvasively' from the body surface, the transducer should have both imaging and therapeutic capabilities. The addition of imaging capabilities will change the geometry of the transducer and the therapeutic capabilities. Studies assessing clinical applications will need to use a transducer with these combined abilities. In addition, the focal point of the transducer used in this study is fixed at the geometric center. A transducer capable of adjusting the focal point will need to be developed.

Previous studies have demonstrated HIFU's ability to deliver therapy through homogeneous tissue without damaging intervening tissue.[3,5,8,9] However, application in infants will necessitate transmission from the subcostal area through tissues with differing absorption properties including skin, subcutaneous fat, liver, diaphragm, pericardium, and cardiac muscle. HIFU has been shown to deliver accurate and reproducible therapy to a fixed target, but the heart is a three-dimensional and dynamic structure. In order to achieve precise spatial localization of the focal zone, a navigation system gated to heart rate will need to be developed. The ideal transducer for fetal or infant hearts will also need a small focal zone, almost certainly necessitating a higher frequency transducer. Future studies will need to address these issues to assess the feasibility of using this technology for clinical applications.

In summary, HIFU is capable of creating defects in cardiac tissues. This technology is potentially a powerful tool in the treatment of congenital heart disease. Further research is necessary to bridge the gap between this ex vivo study and the in vivo application of HIFU.

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