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1. Introduction

Several fetal cardiac malformations have been increasingly treated before birth. Fetal cardiac intervention targets an in utero correction of simple intracardiac abnormalities that potentially progress to complex heart diseases in utero, such as fetal critical aortic stenosis that might cause to hypoplastic left heart syndrome (HLHS) and HLHS with restrictive atrial septum leading to irreversible pulmonary vascular damages (Kohl et al., 2000; Marshall et al., 2004; Makikallio et al., 2006). Current operative procedures for correction of fetal restrictive atrial septum with an atrial decompression are still invasive because they, percutaneously and through both the uterine wall and fetal chest walls, require ultrasound-guided puncture into the frequently-pulsating (120-180 counts per minute) cardiac cavity of tiny fetal hearts and to create interatrial communications. Accordingly, these procedures have been reportedly accompanied by serious complications including profound bradycardia, bleeding and hemopericardium, intracardiac thrombus formation, and recurrent in utero closure of the created atrial septal defects.

To establish fetal interatrial communications with minimal adverse effects, we developed an entirely new approach with the use of high intensity focused ultrasound (HIFU) (Fig. 1). HIFU is acoustic modality using ultrasound energy with cavitation and/or coagulation effect focused to operate on an internally targeted tissue without damaging overlying and/or underlying tissues. HIFU has been employed predominantly for non-touch treatment of tumors including prostate cancer, breast cancer and uterine fibroids (Rebillard et al., 2005; Chan et al., 2002; Hengst et al., 2004). Unlike an extensive ablation of stationary tumors, the HIFU ablation to a frequently-pulsating narrow area in the beating and tiny fetal heart requires highly accurate pinpoint delivery in real-time based on computer-aided auto-tracking of atrial septum.

We developed a new automatic delivery system of HIFU with real-time two dimensional-ultrasound (2D-US) imaging analysis. Features of this system are 1) automatic detection of heartbeat rates, 2) automatic estimation of atrial septum position, 3) automatic generation of HIFU delivery timing and we did feasibility study for creation of an atrial septal defect using the beating heart of anesthetized adult rabbits.
2. Methods

2.1 System configuration

The system configuration of the computer-aided automatic delivery system of HIFU consists of predominantly 5 parts (Fig. 2). The first one is a HIFU delivery device which comprises a monocoque spherical shaped piezo transducer and a diagnostic 2D-US imaging probe mounted on the transducer. The tomographic images are taken by the probe including the focal point of the transducer. The curvature radius of the transducer is 40 mm, and the focal point is located 40-mm apart from the edge face of the transducer. The focal point is an elliptical in shape (0.6-mm wide, 5.0-mm long). The second part is a diagnostic 2D-US imaging equipment (En-Visor C HD, Philips, Andover, MA) to scan a cardiac four-chamber view by 2D-US imaging probe (s12, Philips, Andover, MA). The equipment outputs gray
scale NTSC-video data (640x480 pixels) into the workstation with 30 frames/sec through a video capture (ADVC-55, Canopus, Kobe) and IEEE1394 cable. The third part is a workstation (HP xw8400, Windows XP x64, Intel Xeon 2.33 GHz, Quad Core, 16GB RAM, DirectX9.0c) to analyze an input 2D-US tomographic image of cardiac four-chamber with our original real-time HIFU delivery control algorithm. The workstation detects heartbeat rates, estimates atrial septum positions, and generates HIFU delivery timing by RS-232 interface into a signal transform box automatically. The fourth part is a function generator (Agilent 33220A, Agilent technologies, Santa Clara, CA) to output intermittent sine-wave with certain frequency and voltage into the fifth part, and RF power amplifier (AG1012, T&C power Conversion Inc., Rochester, NY). The timing to drive the transducer by amplified sine-wave is determined by TTL trigger from the signal transform box. Automatic HIFU delivery is accomplished by some adjusting with various parameters. This setting is done through a graphical user interface on the monitor by surgeons (Fig. 3).

![Graphical user interface for setting, adjusting and monitoring of automatic HIFU delivery.](Fig. 3)
2.2 Automatic detection of heartbeat rates

The atrial septum, which is a target of this system to be perforated, repeats expansion, shrinkage and movement with heartbeat. It is assumed that the best timing to perforate an atrial septum safely by HIFU delivery system is when the atrial septum is expanded most. However, because the atrial septum has less features in 2D-US image, it is difficult to detect its movement directly. Therefore, using the fact that atrial septum expands when ventricle contracts, we tried to detect the timing when the left ventricle contracts most, which is easy to detect by 2D-US image. The left ventricular movement of expansion and shrinkage are caused by heartbeats, and its variation can be associated with the change of the left ventricular area in 2D-US image. In this paper, we utilized the automatic detection of the heartbeat period by the following procedures.

1. Setting of Region of Interest (ROI)

We set a rectangular ROI surrounding the left ventricle of 2D-US image on the display while confirming four chamber view of 2D-US image (Fig. 4(A)). ROI should be set so that the left ventricle, which repeats expansion, shrinkage and movement, doesn’t protrude it, and ROI should be the smallest to minimize calculation cost in the image processing.

Fig. 4. (A) Setting of ROI and point of inside the left ventricle (LV). (B) Binary image of 2D-US image, extraction of the left ventricle area and approximate LV ellipse.

2. Pointing of inside the left ventricle

Using 2D-US binarized image by white and black pixels, and the central of inside the left ventricle is pointed by manual in ROI to set target region of the left ventricle to be tracked (Fig. 4(A)). The amount of black pixels which is communicating with the point in ROI is extracted automatically as a left ventricular area.

3. Adjustment of a threshold value in binarization of 2D-US image

2D-US image for the image processing is expressed in gray scale of 256 brightness levels. The threshold value for binarization should be adjusted between 0 and 255 levels so as to extract the left ventricular area adequately. When it is adjusted most adequately, a shape of the left ventricle is approximated an ellipse (Fig. 4(B)). However depending on threshold, the outside of the left ventricle is detected by error and, to the contrary, inside of the left ventricle is not detected. These errors influence precision of the left ventricular area and...
calculation of its geometry described below. Overestimation or underestimation of the left ventricular area causes “undetectable”. In our system the threshold value is adjusted empirically considering actual 2D-US image so that a ratio to be “undetectable” becomes as small as possible.

4. Frequency analysis of the left ventricular area variation

It becomes possible to take samples about variation of the left ventricular area at frequency of 30 times per seconds when the area is extracted adequately. This is because the variation of areas includes heartbeats, low-frequency component by breathing and high-frequency component by noise when 2D-US image is acquired and transferred to the workstation. It is necessary to remove these components by filtering with a small calculation cost. Our system uses the moving average calculation with 8 past samples to remove the low frequency component and the simplicity mean calculation with 2 past samples to remove the high-frequency component. Using fast Fourier transformation the system calculates heartbeat period, frequency and period from 64 past samples without some noises automatically.

2.3 Automatic estimation of atrial septum

As mentioned previously, the atrial septum has less features in 2D-US image which is difficult to detect its position by image processing directly. Therefore the system is set to delivery HIFU only, when position of the atrial septum can be estimated from position and shape of the left ventricle, which is easy to be detected in 2D-US image, and its position corresponds to the focal point of HIFU delivery by a fixed transducer. In this study an automatic estimation of the atrial septum is realized according to following procedures. In addition, the positional information of estimated atrial septum is used as a safety conditional for HIFU delivery based on the allowable error.

1. Position adjustment of HIFU transducer

The transducer and 2D-US probe are fixed physically for one HIFU delivery device. At first, the focal point of HIFU delivery is confirmed precisely by 2D-US image when HIFU is delivering to a low decrement polymer-coated rubber with the acoustic impedance (Acoustic standoff, Eastek Corporation, Tokyo, Japan) that is approximately equivalent to a human body (Fig. 5). The resolution of this 2D-US image around the focus is about 0.5 mm in the direction that throws the beam and about 0.2 mm in the depth direction. We mark a circle to the focal position on this 2D-US image supported by orthogonally-crossed guide lines (Fig. 6(A)). The position and the posture of HIFU delivery device is fixed by manual so that position of the atrial septum corresponds to the focal point of HIFU transducer in the timing when left ventricle shrinks most.

2. Making template information

As well as preceding clause, we mark a cross on the atrial septum of the timing when the left ventricle shrinks most by manual operation and define the coordinate with (XAt, YAt). In addition, we define the fillet diameter of the left ventricle shape approximated by a ellipse with (RXt, RYt) and the coordinate of center of gravity position with (XGt, YGt), and use these parameters for the image analysis in the next clause as template information to estimate the atrial septum position (Fig. 6(B)).
Fig. 5. Confirmation of ablated focal point by HIFU delivery on 2D-US image. Ablated focal point is ellipsoid of 5-mm long and 2-mm wide.

Fig. 6. (A) Pointing focus of HIFU with X-Y guide lines on the 2D-US image. (B) Determination of template parameters by pointing of atrial septum and getting fillet radius.
of approximate LV ellipse (RXt, RYt) and its center of gravity (XGt, YGt) when the left ventricle is minimum. (C) Automatic estimation of atrial septum position (XA, YA) with geometric ratio between current information (fillet radius and center of gravity position) and template parameters. If estimated position is in the error margin circle of HIFU focus, HIFU delivery is allowed.

3. Geometric estimation of the atrial septum position

Using the left ventricular fillet diameter (RX, RY) and the geometric center of gravity position (XG, YG) detected in 30 frames per seconds, template fillet diameter (RXt, RYt) and template geometric center of gravity position (XGt, YGt). We estimate current atrial septum position (XA, YA) by formula (1) automatically (Fig. 6(C)). HIFU delivery is permitted only when the position (XA, YA) is in a circle around (XAt, YAt) for allowable error.

\[
\begin{align*}
    X_A &= X_G + (X_{At} + X_{Gt}) \times \frac{RX}{RXt} \\
    Y_A &= Y_G + (Y_{At} + Y_{Gt}) \times \frac{RY}{RYt}
\end{align*}
\]  

(1)

2.4 Definition of HIFU delivery timing

It is determined the timing when HIFU should be delivered by analysis of the four chamber view in 2D-US image. However, there is the delay time (TD) constantly between acquisition of 2D-US image, image transformation by the video capture, image analysis with the workstation, trigger output to a function generator, sinusoidal amplification in the RF power amplifier and HIFU delivery by a transducer. It is about 33 ms in this system, which is just equal to the delay for 1 frame of 2D-US image. Therefore based on the image analysis results HIFU delivery is enabled the timing when the left ventricle shrinks most by the trigger of HIFU delivery at the time of “TS-TD”, which deducted the delay time from the predicted time that left ventricle shrinks most (TS) (Fig. 7).

Fig. 7. Definition of HIFU delivery starting trigger timing with total delay time in the system. The timing is the delay time TD before the timing TS that the left ventricle area will be minimized locally.
2.5 Security condition for HIFU delivery

HIFU delivery is conducted based on the timing when the left ventricle shrinks most in consideration of the delay time in the system. In order to avoid some issues, caused by various factors and disturbances, to deliver HIFU outside of the allowable circle. The system is permitted to deliver HIFU as far as meeting following security conditions so as to avoid "shooting by mistake", which means that HIFU delivery is outside the allowable limit of error radius and ablated point is overshoot the actual atrial septum, even if the point is inside the allowable limit of error radius (Fig. 8).

Fig. 8. Monitoring of HIFU delivery condition defined by focal accordance, area of LV, heartbeat synchronous and circularity of LV.

1. The upper limit of movement distance of the left ventricular geometric center of gravity
2. The maximum value of the left ventricle area
3. Success or failure of the heartbeat cycle detection by fast Fourier transformation
4. The minimum value of the ellipsoid roundness, which is approximate shape of the left ventricle
5. Whether an estimated position of the atrial septum is inside focal allowance limits of error or not

These conditional thresholds are settable individually, and we can select any conditions. Delivery frequency decreases if the conditions are strict. On the other hand, it increases if
the conditions are easy. However, we have only a rough index for optimal parameters because individual difference is large by the delivered target of HIFU. Therefore, it is necessary to judge during securing safety as the trigger off for HIFU delivery while watching the temporal change in HIFU delivery condition on the display whether you can irradiate it more effectively, the parameters are appropriate, or more effective delivery is possible.

3. In vivo experiment

3.1 Purpose

In this experiment, we confirmed feasibility of our computer-aided automatic delivery system of HIFU to perform atrial septal defect creation of animals in vivo. We used four healthy animals (Japanese white rabbit, male, 2.8 kg) with cardiac pulsation under anesthesia. Their bodies are slightly larger than our practical target fetus.

3.2 Methods

We tested HIFU delivery to adult rabbits of which limbs were fixed to the operating table. This is because it was covered by flat breast bone, and HIFU reflected the heart of the rabbit. We tried HIFU delivery in a state exposed with rabbit’s heart by a median section and under the environment that which heart moves during the pulmonary respiration by the respirator unlike intrauterine fetuses. In the case of practical intrauterine fetuses, their undeveloped breast bone does not damp HIFU and they don’t breathe with lung. We performed this experiment in the following procedures strictly in accordance with the rule that the animal executive committee in National Center for Child Health and Development.

1. Four adult rabbits (Japanese White, 2.8 kg, male) were anesthetized with xylazine (5 mg/kg IM) and isoflurane by inhalation.
2. After endotracheal intubation or tracheostomy placement, anesthesia was maintained on the mechanical ventilation with isoflurane and oxygen inhalation (20 cycles/min, 240 ml/cycle).
3. ECG, arterial blood pressure/oxygen saturation, and end-tidal carbon dioxide concentration were monitored intraoperatively in real time.
4. The animals underwent median sternotomy to expose the heart, chest cavities were filled with buffering gel on both sides. The heart beats was set in the direct contact with a silicone sheet-bottomed tank filled with degassed water (37°C) (Fig. 9).
5. A HIFU transducer combined with a diagnostic 2D-US imaging probe was fixed on a two-directional (X-Y) linear stage with a pivot hinge placed on the tank which was manually steered, so that the HIFU focal point could be roughly located on the atrial septum of the beating heart.
6. Various parameters for HIFU delivery were specified.
7. Automatic HIFU delivery was carried out with this system.
8. After HIFU delivery, we confirm whether new blood flows is generated across the atrial septum using color Doppler echocardiography by the diagnostic 2D-US imaging equipment.
9. After this experiment, we inject pentobarbital into a peripheral venous path and sacrifice the rabbits.

![Fig. 9. Experimental setup using an adult rabbit. HIFU delivery was done through a silicone sheet at the bottom of the degassed water tank.]

### 3.3 HIFU delivery condition

The waveform output from a function generator is observable with an oscilloscope, which is amplified by RF power amplifier and is input to a transducer. In this experiment, the input waveform was sine wave of 3.3 MHz, 160 Vpp and 6.5 kW/cm².

For the total HIFU delivery time in one trial, we set three seconds from experiences of the prior pilot study. The allowable limit of error radius of HIFU delivery spot is set to the same value in all trial so that it was with the smallest circle which a focus shape of HIFU was fit into on a display.
Fig. 10. Heart specimens ablated with HIFU delivery. Left images are gross appearances of the inadvertent ablation with opening. Right images are magnifications of the area ablated by HIFU deliveries. (A) A small opening was made in the posterior wall of the left atrium. (B) Atrial septum apparently remained non-penetrated with mere coagulation changes. (C) Non-penetrated small hole was made on the atrial septum with hematoma formation. (D) Non-penetrated small hole was made on the atrial septum accurately.
The HIFU delivery began at the moment when a surgeon pushed the button for beginning of automatic delivery on a display and came back to the standby state when 3-seconds HIFU delivery was completed in total.

3.4 Results
Four rabbits were euthanized after HIFU delivery, and dissected their isolated hearts and observed around the atrial septum (Fig. 10(A) - (D)). In the first trial, it took 23 seconds from beginning of automatic HIFU delivery to the end (Fig. 10(A)). The penetration of the tissue in the chamber was completed, however the position was missed from the atrial septum toward posterior parietal side, which is the left atrium side. In the second trial, it took 57 seconds by the end (Fig. 10(B)). A cauterization spot was found on the atrial septum in pinpoint, however the HIFU delivery did not achieve a penetration. In the third trial, it took 44 seconds by the end (Fig. 10(C)). The perforation on the atrial septum was confirmed, however it did not achieved a penetration. In addition a hematoma-like change was found beside a perforation spot. In the last trial, it took 46 seconds by the end (Fig. 10(D)). The perforation on the atrial septum was confirmed, however it did not achieve a penetration. Unlike the third trial the hematoma was not found.

4. Discussion
In this study, we developed automatic delivery system of HIFU based on real-time 2D-US imaging analysis. In in vivo experiment we confirmed pinpoint delivery of HIFU to the pulsating atrial septum within beating hearts of anesthetized adult rabbits.

In the field of cardiology, HIFU was investigated as a promising device to treat arrhythmia, relieve valvular stenosis and ameliorate obstructive hypertrophic cardiomyopathy. HIFU also enables us to create defects in cardiac tissues such as ventricles or cusp of the aortic valve in vitro or ex vivo (Otsuka et al., 2005; Fujikura et al., 2006; Lee et al., 2000; Xu et al., 2004; Strickberger et al., 1999). Particularly in fetal cardiac intervention, less invasiveness of HIFU is effective for the mother as well. In addition, HIFU delivery can be a actual operative method with security, a short time and low cost. Our new system is useful for an approach into the heart chamber with more safety owing to detection of a heartbeat cycle only from 2D-US four chamber view without other measurement instruments and estimation of atrial septum position pulsating with heartbeats and breathing for more effective HIFU delivery.

4.1 Detection of heartbeat
In order to obtain heartbeat information, it is common to use an electrocardiogram (ECG). There is a reported study to try the treatment of arrhythmias using the HIFU delivery triggered by ECG (Strickberger et al., 1999). However, it is difficult to isolate only ECG of fetus from a maternal ECG definitely although fetal ECG monitoring is technically quite demanding because ECG of fetus is obtained only through the mother. Therefore, the method to detect the heartbeat cycle of fetus only from real-time 2D-US image in our system is thought to be appropriate for clinical application from convenient point of view. However, based on the image processing, the amount of calculation is larger and delay time
is longer than ECG signal analysis. This is because arrhythmic development is expected, and heartbeat cycle collapses with a diseased heart. It is better that the delay time is short to detect arrhythmic development quickly. We had a plan to introduce the system with fetal ECG together in near future.

4.2 Estimation of atrial septum

About the estimation of the atrial septum position, although the surgeon confirmed it by monitoring before HIFU delivery in vivo experimental qualitatively, ablated point was not so overshot the atrial septum, of which position was estimated from 2D-US image. However, when the 2D-US image was not clear, the left ventricular position and shape were not obtained precisely. There were some cases that estimation of the atrial septum was impossible. Consequently, HIFU delivery was not permitted by security conditions in this case. We were able to avoid shooting by mistake outside the allowable limit of error radius in 2D-US image. Also, we calculated geometric ratio between the left ventricular center of gravity position and the approximate fillet diameter for “correct answer” which a surgeon sets by manual operation as template information, however the procedure is limited on 2D plane. We don’t consider that the heartbeat includes movement and transformation (expansion, shrinkage and distortion) not only in 2D plane (X-Y plane), but also in the depth direction (Z-axis direction). It depends on how detection of the heartbeat and the estimation of the atrial septum position are accurate what appropriate four chamber view is acquired. The detection of the heartbeat from the extraction of the left ventricular area on 2D-US image is no more than approximation. Even if the focal point is inside allowable limit of error radius in 2D-US image, the HIFU delivery results in shooting by mistake three-dimensionally because prior confirmation of the HIFU focal size and shape, fixation of the HIFU delivery device, and setting of the parameters about HIFU delivery condition were performed on the basis of 2D-US image only. This is the major reason of the HIFU delivery position error. For the solution of this issue, at least when HIFU delivery device is fixed on target we should use a three-dimensional ultrasound (3D-US) probe to recognize detail of 3D positional relationship between the focal point and the actual atrial septum in beating heart for more accurate focal position alignment. It is expected that performance of the 3D-US diagnostic equipment improves to acquire and analyze 3D-US voxel data in real time directly, which leads drastically higher precision of HIFU delivery with our system in near future.

In addition, the real intrauterine fetus is floating in the amniotic fluid and is movable three-dimensionally. During surgery, the fetus doesn’t exercise spontaneously because both mother and fetus are under anesthesia, however we have to track not only movement of the atrial septum but also the fetal movement of oneself. That is to say in addition to 2D-US for four chamber view of the heart. We need 3D-US to track movement of intrauterine fetus three-dimensionally. At the same time it is important to move HIFU delivery device itself mechanically to track fetal wide movement in utero (Koizumi et al., 2008).

4.3 In vivo experiment

We tried HIFU delivery to the animals which imitated intrauterine fetuses, however the results didn’t achieved both delivery efficiency and delivery accuracy of HIFU. The only
one trial perforated tissue in the beating chamber, and the perforated point was on the adjacent tissue of the atrial septum. On the other hand, the three trials ablated just the atrial septum, and no perforations were generated. The HIFU delivery efficiency depends on the ratio of delivery time in one heartbeat and the total time to complete preset HIFU delivery in each trial. In all trials, we set the same delivery conditions on a respirator, size (weight) of the animal, the allowable limit of error radius around HIFU focal point, and the total HIFU delivery time. However, there were individual differences in animals’ heartbeat cycle and 2D-US image of the left ventricle, and also, we found small differences in relative position relationship between animal body and HIFU delivery device because we made adjustments to delivery setting in each trial. Therefore, the variation occurred in the total time to complete preset HIFU delivery in each trial. To increase the safety, the shorter delivery ratio in one heartbeat and more strict security conditions are required. However, if the total time lead to longer to complete preset HIFU delivery, the one HIFU delivery interval gets longer, which results in no perforation of the tissue due to diffusion of converged HIFU energy into intracardiac blood flow. HIFU delivery frequency around 3.3 MHz may cause heating effect and/or mechanical (cavitation) effect. If the perforation of tissue is caused by only mechanical effect of cavitation, we need not consider the diffusion of the HIFU energy in to the blood flow. In order to avoid cooling effect by the blood flow, it is more useful to take advantage of mechanical effect of cavitation positively. However, it is necessary to progress clarification about which is dominant heating effect or mechanical effect of cavitation by detailed simulation and local observation around the focal point. When heating effect is dominant, we should lengthen the delivery ratio in one heartbeat to raise HIFU delivery efficiency and make continuous HIFU delivery by loose of security conditions. However, the security of HIFU delivery tuens down by contraries and the possibility is reduced to be delivered in the point that we aim at. Assurance of security is in a relation of the trade-off with HIFU delivery efficiency, and balancing both is not easy. For safe and secure HIFU delivery we will progress further validation to investigate optimal HIFU delivery conditions from both hardware and software point of view.

5. Conclusion

We developed computer-aided automatic delivery system of HIFU for creation of an atrial septal defect which perforates tissue in the intracardiac chamber for less invasive cardiac intervention of intrauterine fetuses. In vivo experiment using animals, by only 2D-US image of four chamber view, it was possible to detect heartbeat period, estimate the atrial septum position, and determine HIFU delivery timing in real-time under heartbeats.

In near future, we will aim at the clinical application as a minimal invasive surgical system in order to improve precision improvement of the focus positioning of HIFU delivery and improvement of HIFU energy efficiency to intracardiac tissue.

6. Acknowledgement

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7. References


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Atrial Septal Defects (ASDs) are relatively common both in children and adults. Recent reports of increase in the prevalence of ASD may be related use of color Doppler echocardiography. The etiology of the ASD is largely unknown. While the majority of the book addresses closure of ASDs, one chapter in particular focuses on creating atrial defects in the fetus with hypoplastic left heart syndrome. This book, I hope, will give the needed knowledge to the physician caring for infants, children, adults and elderly with ASD which may help them provide best possible care for their patients.

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