**Transesophageal cardiac ablation using High Intensity Focused
Ultrasound: A new minimally invasive therapy for treating arrhythmias**

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Introduction

Transesophageal HIFU probes were designed to ablate heart tissues thermally. The project had two main goals:

- Demonstration of the feasibility of thermal lesion production in realistic heart models
- Development of the passive elastography as a treatment monitoring technique for HIFU application in the heart

Passive elastography was proposed to assess the thermal damages obtained during *in vivo* and *ex vivo* trials and compared with conventional radiation force elastography (SSI) and MRI. Midterm report described the development of the software interface, *in vitro* dosimetry study, initial progress on passive elastography and *in vivo* preliminary analysis of baboon hearts. In the present report, the results of the *in vivo* trials on baboons will be presented with extended developments on elastography. The exposure conditions will be also optimized using *ex vivo* beating models.

Material and results

Passive elastography

Shear-wave elastography is an imaging method that maps the stiffness of tissues, related to the shear-wave velocity. For the *in vivo* experiments on baboons, two different methods of shear-wave elastography were used. First, Supersonic Shear-wave Imaging (SSI), also named radiation force elastography, is already used in clinic for the diagnostic of breast cancer or cirrhosis [1]. It was already evaluated with our transesophageal probe [2] and will not be described in details.

The second method is the passive elastography [3]. Instead of tracking externally generated shear-waves (SSI), passive elastography uses natural noise-like shear-waves already present in the body. Previous researches demonstrated the natural presence of strong shear-waves in the myocardium, produced by the opening and closure of the heart valves [4]. We proposed here to apply passive elastography for monitoring the thermal lesions. Beside the natural occurrence of shear-wave in the heart, this choice was motivated by the difficulty of generate shear waves in depth for SSI. Indeed, because SSI technique produced an ultrasonic push with the imaging probe, power output needed for the radiation force is limited by the absorption of the tissues. This strongly affects the range of imaging depth of the SSI. Passive elastography is no longer impacted by this limitation and is only influenced by the B-mode imaging capabilities.

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Development of the Passive Elastography on the transesophageal probe

To image the shear-waves propagation in the heart, Pappadacci et al. showed that a high frame rate of ~1000 fps is required [5]. Standard B-mode acquisition sequences are limited to ~60 fps. A diverging wave sequence with coherent compounding was developed for our TEE probe.

According to the literature, a 700-1000 fps acquisition with 5 angles per frame was programmed on a Vantage 256 Verasonics machine (Verasonics, Kirkland, WA). The quality of the sequence was tested on a calibrated B-mode phantom (CIRS, Norfolk, VA). Comparison between standard B-mode acquisition (128 rays, 60 fps) and programmed diverging acquisition is presented in the figure 1.

Standard B-mode

Diverging wave – 1 angle

Diverging wave – 31 angles

Fig. 1: Example of imaging of CIRS phantom

After programming ultrafast acquisition, passive elastography was tested *in vitro* in liver. The sample was immersed in a water tank at 37°C. The transesophageal probe was then placed in front of it with the focal point positioned 1 cm deep in the tissues. The sample was sonicated for 16 s with an acoustic intensity of 7 W/cm² at the surface of the transducer. Pre- and post-insonication elastography acquisitions were done (500 ms long, 1000 fps). *In vitro*, noise-like shear-waves were produced with vibrating pot (chirps 50-500 Hz) positioned at the surface of the sample. Figure 2 presents the passive elastography performed before and after the insonication and the corresponding gross pathology. The lesion is clearly visible on post-ablation elastography map. The dimensions of the lesion measured by elastography and pathology were consistent: ~1 cm in length, thickness of 3 mm for the elastography and 5 mm for the gross pathology.

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Figure 2: Example of passive elastography in vitro in a pig liver showing the ablated zone consistent in dimensions with gross pathology.

Influence of the motion on the passive elastography

Currently, passive elastography used acquisition sequences which are 500 to 1000 ms long. Consequently, heart beat can strongly corrupt passive elastography results. Experiments on a calibrated phantom were conducted in order to account for the heart motion. The phantom (CIRS elasticity) was immersed in water. Shear-waves were produced by audio speakers placed on its surface. A L7-4 linear array was placed on a slow linear motor to simulate a linear repetitive motion normal to the surface. Applied motions were from 0 to 3.8 mm with a velocity from 0 to 46.3 mm/s. Ultrafast acquisitions

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were performed for a 600 ms long period with 1000 fps with a Verasonics imaging device. Four post-treatment methods were tested to process experimental data. The first one was the basic application of passive elastography. The second one consisted in filtering the low frequency on the noise-like shear-waves to suppress slow motion (typically frequency of 1-10 Hz in the case of the heart motions). The third one consisted on the selection of the non-moving period of the cycle. The last one used the registration to cancel motion.

Results showed that the third method gave a good result in terms of geometry (Figure 3). The combination of the registration and the filtering can also improve significantly the quality of the mapping. However, this method need heavy computation modalities and thus may be hard to apply. However, imaging during the non-moving part of the cycle may be complicated with the absence / reduction of shear-waves during this period.

Fig. 3: Normalized shear-wave velocity maps of an elastography CIRS phantom.

In vivo trials

Goals of the study

The goal of the study was to demonstrate the feasibility of the creation of thermal lesions inside heart myocardium on a realistic model like the baboon with a transesophageal probe. Three goals were defined:

- Creation of a precise thermal ablation in the myocardium under ultrasonic guidance
- Monitoring of the thermal lesion with SSI and passive elastography and comparison with MRI.
- A mid-term follow-up at six months

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The experimentation was performed in three steps:

- Step 1 (Day 1): treatment planning and *in vivo* model analysis
- Step 2 (Day 2): Cardiac thermal ablation procedure with ultrasonic monitoring
- Step 3 (Day 3): Postoperative evaluation with MRI at 24 h

The experiments were conducted on three 30 kg male baboons. The physical dimensions of the esophagus and the heart are close to those of humans. The local ethic committee and the Ministry of Research approved this animal experimentation under the agreement #04931.02.

Treatment Planning and *in vivo* Model Analysis

This part was described in the mid-contract report and concerned the first subject. We demonstrated the feasibility of the insertion of the probe and the targeting of different zones of the heart.

The two other subjects allowed confirming these initial observations. Inserting the probe in the esophagus of the second baboon was more challenging. But no damage was observed on this subject right after treatment and during the follow-up period. Additionally, it was demonstrated that the position of the animal had a significant impact on the feasibility of the treatment. Two CT-scans were done with the subject #2 in supine and left lateral positions.

Superposition of both acquisitions showed a significant shift of the heart axis depending on body position (Figure 4). The pre-operative imaging and treatment have to be performed with the same animal posture.

Fig. 4 : Superposition of CT-scans performed in supine and left lateral positions. The shift of the heart inside the thoracic cavity is clearly visible.

Ablation Procedure

After anesthesia and intubation, apes were positioned in left lateral decubitus. No anti-arrhythmic and β - blocker drugs were used during the trials. The HIFU probe was inserted without any

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problems on the three subjects. First inspection of the structure was made using ultrasound imaging with the transesophageal probe. Because the TEE probe of the prototype is not motorized (transverse imaging plan only), the analysis of the heart muscle is more delicate than with a clinical TEE device. Targeted zones were then confirmed (Figure 5).

Fig. 5: Targeted area on 3D heart model. (1-4) inter-atrial septum (2) Left wall of the left atrium (3) Antero-posterior part of the left ventricle.

The targeted zones were mainly:

- Inter-atrium septum
- Left wall of the left atrium
- Basal annulus and high antero-posterior part of the left ventricle

Insonication parameters were 16 s continuous shots of 7.1 W/cm², repeated 4-15 times. No lesions on the esophagus were visible after sonicating the three subjects.

Elastography Monitoring

Elastography acquisitions were done before and after HIFU ablation with a research Aixplorer imaging machine (Supersonic Imagine, Aix-en-Provence, France). Two kinds of acquisitions were done: 1000 ms ultrafast (1 kHz) continuous diverging wave imaging for the passive elastography and radiation force elastography with acquisitions during diastolic period. Ultrasonic pushes created for the SSI were produced with the TEE probe.

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Stiffness modifications were observed on the subject #1 on the high latero-posterior part of the left ventricle after HIFU with both elastography methods (Figure 6). A stiffening of the tissue was visible between pre-and post-acquisition of passive elastography (Method #3 with gating - 30% increase of the wave length). This result was confirmed by SSI (SWE) elastography with a two-fold increase of the stiffness. It should be noted that the SSI was not able to map the stiffness but only measure the average elasticity. It was mainly due to the distance between the TEE probe and the zone of interest. No change was visible on the two other subjects through elastography.

Fig. 6: Passive and radiation force elastographies of the antero-posterior wall of the left ventricle of the first subject. No change of the echogenicity was measured by echography.

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MRI lesion evaluation

MRI is considered as the gold standard for assessing the presence of thermal lesions inside heart muscle and is used for following thermal ablation induced with a catheter (radio frequency or cryoablation). 24 h after ablation procedure, subjects were anaesthetized using ketamine and medetomidine. Anesthesia continued with isoflurane. Two sequences were used: T1-weighted and T1 with gadolinium.

On the high latero-posterior part of the left ventricle of the first subject, mild hypersignal was visible on the T1 weighted acquisition (Figure 7). It corresponds with the zone of stiffness increase on elastography. No change was visible on the T1 with gadolinium.

Gadolinium

Weighted T1

Fig. 7: Visualisation of the left ventricle of the first subject. T1 with gadolinium on the left and T1 weighted image on the right. Mild hypersignal zone showed with the red arrow.

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Midterm Follow-up

Baboons returned to their facilities 24 h after MRI and were followed for six months. Subjects recovered completely of the different procedures. No undesired events occurred during the follow-up. After six months, no evidence of complications, such as arrhythmias or fistula, was found.

Conclusion

These first experimentations tend to demonstrate that HIFU lesion can be induced in a beating heart with a transesophageal probe. However, the efficacy of the treatment could not be guaranteed. It is not clear also whether the imaging methods were not sensitive enough or the treatment was not efficient enough. For ethical considerations, histology could not be performed. For sure, the trials showed the clinical safety of the insertion of the probe and the ablation procedure itself and no side-effects evidenced after six months.

In order to improve the efficacy of the treatment and the sensitivity of the elastography, more experiments were performed *ex vivo* on a beating heart.

Ex Vivo Trials

To enhance the heating capability of the device, new insights on the HIFU parameters were done. For the *in vivo* trials, the sonication parameters were derived from trials on swine which used continuous exposures [6]. With this probe, the maximal acoustic intensity was limited to 7 W/cm² in order to maintain the surface temperature below 65 °C. The sonication had to be regularly interrupted to allow the temperature of the transducer to drop (each 16 s for ~ 4 s). Moreover, because of the continuous sonication and tissue motions, the energy was not delivered in a narrow zone. To increase power output and improve energy delivery, the sonication was synchronized with the heart rhythm. To do so, the diastolic period during the heart cycle was aimed. Diastolic period is the period with less heart motion and corresponds to 50% of the whole cycle. With this new technique, for the same delivered energy, no pause was needed, while staying into acceptable temperature range for the probe.

Five sheep *ex vivo* hearts were used to test these new parameters. After surgical extraction, *ex vivo* hearts were perfused with the Langendorff technique [7]. This technique permits reperfusion of the tissue and ensures heart motion. Hearts and the prototype were placed in a tank filled with water at 37 °C. The targets were located in both ventricles, the IV septum and the apex and ranged in thickness from 0.5 to 2 cm. The number of sonications was set according the thickness of the target (1 to 5). Each

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sonication lasted 2.5 min. On the first heart, continuous sonications were delivered. On the four others, synchronization between sonications and heart beat were done by pacing electrically heart muscles. Each sonication lasted 5 min with a 50% DC. Passive elastography was tested on the last *ex vivo* heart (Method #3). After ablation procedure, MRI evaluation was done (T1 and T2 weighted). MRI was done without the reperfusion. So, gadolinium could not be used. Then, pathology was performed.

Considering transmural tissue denaturation visible on the gross pathology as a success of lesion production, without any synchronization with the heart rhythm, only 8% success rate was reached on the 12 sonicated sites. When synchronizing, the success rate increased to 40% for the same emitted energy on the 5 sonicated sites. Synchronization allowed better cooling of the HIFU transducer during the sonications. Thus, the acoustic intensity could be increased from 7 to 12 W/cm² while preserving the transducer from extensive heating. With this new power output, a 100% success rate could be achieved on the 7 sonicated sites (Figure 8).

Fig. 8: Success Rate evaluated with Gross Pathology

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Lesions were also visible on MRI. For instance, on the figure 9, a transmural lesion made of four sonications in the left ventricle is presented. With the T1-weighted image (on the left), this lesion is clearly visible and confirmed by the T2-weighted image (on the right). It can be noted that the hypersignal due to the lesions are weaker because the non-perfusion during the MRI evaluation affects the sequence acquisition which is designed for *in vivo* conditions.

Fig. 9: Gross pathology and MRI of a thermal lesion in the left ventricle produced with 4 sonications of 5 min synchronized with 50% of the heart cycle with an acoustic intensity of 12.1 W/cm² on the surface of the transducer.

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On the last two hearts, passive elastography was also tested. Acquisitions of 700 ms with 1000 frames per second were done before and after sonication. As shown in the figure 10, lesion is clearly evidenced after the sonication by a strong stiffening of the tissue. It confirmed the capability of passive elastography for lesions monitoring.

Fig. 10: B-mode, passive elastography and gross pathology of a thermal lesion in the right ventricle produced with a 5 min shot synchronized with 50% of the heart cycle with an acoustic intensity of 12.1 W/cm² on the surface of the transducer.

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Conclusion

In vivo experiments on three baboons demonstrated the safety of the procedure and its clinical feasibility. It also evidenced the need to improve the delivery of energy. Sequences for passive elastography were designed for the transesophageal prototype. Experiments on phantom demonstrated the ability of passive elastography to work on moving organs. HIFU parameters were optimized on five *ex vivo* Langendorff hearts to improve the repeatability of the technique. Thermal lesions could be systematically created. They were clearly visible on elastography and MRI modalities. Those new parameters will be used in further *in vivo* trials. These results obtained with the support of the FUS Foundation helped to obtain a significant follow up grant from the French National Agency for Research in order to improve the technology and get closer to the clinic. The consortium gathers experts in ultrasound technology (LabTAU in Lyon), ultrasonic medical device (the company Vernon in Tours), cardiac procedures and MRI (Lyric in Bordeaux) and signal and image processing (LTSI in Rennes).

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