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Fast lesion mapping during HIFU treatment using harmonic motion imaging guided focused ultrasound (HMIgFUS) *in vitro* and *in vivo*

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Abstract

The successful clinical application of high intensity focused ultrasound (HIFU) ablation depends on reliable monitoring of the lesion formation. Harmonic motion imaging guided focused ultrasound (HMIgFUS) is an ultrasound-based elasticity imaging technique, which monitors HIFU ablation based on the stiffness change of the tissue instead of the echo intensity change in conventional B-mode monitoring, rendering it potentially more sensitive to lesion development. Our group has shown that predicting the lesion location based on the radiation force-excited region is feasible during HMIgFUS. In this study, the feasibility of a fast lesion mapping method is explored to directly monitor the lesion map during HIFU. The harmonic motion imaging (HMI) lesion map was generated by subtracting the reference HMI image from the present HMI peak-to-peak displacement map, as streamed on the computer display. The dimensions of the HMIgFUS lesions were compared against gross pathology. Excellent agreement was found between the lesion depth ($r^2 = 0.81$, slope = 0.90), width ($r^2 = 0.85$, slope = 1.12) and area ($r^2 = 0.58$, slope = 0.75). *In vivo* feasibility was assessed in a mouse with a pancreatic tumor. These findings demonstrate that HMIgFUS can successfully map thermal lesions and monitor lesion development in real time *in vitro* and *in vivo*.
in vivo. The HMIgFUS technique may therefore constitute a novel clinical tool for HIFU treatment monitoring.

Keywords: HMI, HMIgFUS, lesion quantification, fast lesion mapping, real-time HIFU monitoring

(Some figures may appear in colour only in the online journal)

Introduction

High intensity focused ultrasound (HIFU) ablation is a noninvasive treatment procedure which delivers a large amount of energy, causing a localized temperature rise and cell necrosis. Numerous studies and clinical trials have used HIFU to treat local diseases in organs such as the thyroid, prostate, breast, pancreas and liver (Jang et al 2010, Warmuth et al 2010, Esnault et al 2011, Wijlemans et al 2012, Peek et al 2015). The clinical translation and accessibility of HIFU relies heavily on improving its treatment monitoring.

There are several techniques currently being investigated to detect the real-time treatment performance of HIFU. Magnetic resonance imaging (MRI) thermometry (McDannold et al 2000, Dibaji et al 2014) is used to detect the temperature rise across the treatment area. However, MRI guidance can be expensive and time-consuming compared to ultrasound-based HIFU guidance; the temporal resolution for this clinical application is usually between two and six s (Wijlemans et al 2012). Among the ultrasound guidance techniques, conventional B-mode-based ‘hyperecho’ tracking can be challenging for HIFU monitoring as it is sensitive to air bubbles, which occur at high temperatures and usually lead to over-treatment of the targeted region (Ueno et al 1990, Yu and Xu 2008). Passive acoustic mapping has also been investigated regarding its capability of monitoring HIFU ablation by reconstructing the emissions generated by inertially cavitating bubbles during HIFU. However, the estimates of cavitation location and intensity are also prone to errors due to the limited axial resolution (Jensen et al 2012, 2013).

Over the past two decades, ultrasound elasticity imaging has expanded from a diagnostic technique to include therapy guidance and monitoring based on tissue stiffness change (Souchon et al 2003, Thittai et al 2011, Kwiecinski et al 2015). Compared to bubble- or cavitation-based methods, elasticity imaging does not rely on, or is affected by, boiling air bubbles formed at the focus but instead monitors the change in the tissue characteristics. However, most elasticity imaging techniques require HIFU to be interrupted for reliable monitoring, and therefore cannot detect the onset of lesion formation in real time, significantly increasing the treatment duration and cumulatively reducing the efficiency of a HIFU treatment.

Harmonic motion imaging (HMI) is a radiation-force-based ultrasound elasticity imaging technique which is designed for both tissue relative stiffness imaging and reliable HIFU treatment monitoring. An amplitude-modulated (AM) HIFU beam is transmitted through a focused ultrasound (FUS) transducer to induce tissue vibration at the focal region. The oscillatory response from the tissue can be tracked using radio-frequency (RF) signals acquired with a confocally-aligned imaging transducer (Konofagou and Hynynen 2003, Maleke and Konofagou 2008). The oscillatory displacement amplitude, namely the HMI displacement, is monitored continuously to provide real-time tissue stiffness change during the treatment. Without interrupting the ablative procedure, HMI guided FUS (HMIgFUS) can be applied with optimal efficiency to the targeted area. Several studies have been published showing the feasibility of HMI on post-surgical human breast tissue (Han et al 2016), ex vivo canine liver
(Hou et al 2014b, Han et al 2015) and in vivo mice (Chen et al 2015, Payen et al 2016). A fast imaging and processing algorithm is essential to ensure real-time lesion mapping. Recently, HMI was shown to be capable of streaming HMI displacement in real time at 15 frames s\(^{-1}\) (Grondin et al 2015). Although the oscillatory HMI displacement contains important information on tissue stiffness change, it does not provide information on the lesion location or lesion size itself in real time. A fast lesion mapping method that can inform physicians intuitively on the progression of thermal lesioning in real time without sacrificing the frame rate is thus wanted.

Our objective in this study is first to develop a HMIgFUS-based lesion quantification method to map and quantify HIFU-induced thermal lesions. We also aimed at demonstrating the accuracy as well as reproducibility of the lesion quantification method through gross pathology validation in vitro and in vivo. Finally, we aimed at implementing a fast lesion mapping method for online processing to achieve lesion formation monitoring during HMIgFUS treatment in real time.

Methods and materials

HMI

In HMI, the radiation force generated at the focal region can be expressed with equation (1) with the assumption of attenuating a homogenous medium and linear plane wave propagation (Torr 1984, Starritt et al 1991):

\[
F = \frac{2\alpha I}{c}
\]

where \(F\) is the radiation force generated (N m\(^{-3}\)), \(\alpha\) is the tissue absorption coefficient (m\(^{-1}\)), \(I\) is the temporal average acoustic intensity (W m\(^{-2}\)) and \(c\) is the sound speed (m s\(^{-1}\)). With the amplitude modulated at the frequency \(\omega_m\) on the HIFU beam, an oscillatory radiation force is generated at the focal region to vibrate the tissue at \(\omega_m\), which is 100 Hz in this study. The oscillatory displacement is monitored continuously through a phased array imaging transducer. The changes in the estimated displacement amplitude can be used to indicate the relative stiffness change when the lesion is starting to form at the focal region.

HMIgFUS

Figure 1 shows an illustration of the experiment setup. The HMIgFUS system consisted of a FUS transducer and a phased array imaging probe coaligned through the central opening (diameter = 41 mm) of the FUS transducer. The FUS transducer was a 93-element phased array (\(f_c = 4.5\) MHz, and \(D = 70\) mm, Sonic Concepts Inc., Bothell WA, USA). The imaging probe was a 64-element phased array (\(f_c = 2.5\) MHz, P4-2, ATL/Philips, Bothell, WA, USA). A dual-channel arbitrary waveform generator (AT33522A, Agilent Technologies Inc. Santa Clara, CA, USA) was used to generate an AM sinusoidal signal to drive the FUS transducer through a 50 dB power amplifier (325LA, E&I, Rochester, NY, USA). The imaging probe was inserted through the central opening and confocally aligned with the FUS transducer. The imaging probe was transmitted and received through an ultrasound imaging research system (Vantage, Verasonics, Bothell, WA, USA) with a pulse repetition frequency (prf) at 1000 Hz. The FUS total output acoustic power was within the range of 6.4–8.6 W from radiation force balance measurements (Hynynen 2011). A T-type bare wire thermocouple with a diameter of
80 μm (Physitemp Instruments Inc., Clifton, NJ, USA) was inserted into the tissue and aligned with the focal spot for temperature monitoring at the focal region.

Real-time HMIgFUS and displacement estimation

During real-time HMIgFUS, the RF channel data was acquired at a prf of 1000 frames s⁻¹. In order to calculate the peak-to-peak HMI displacement without sacrificing the display frame rate, only ten consecutive frames within a single HMI vibration were obtained at each acquisition and transferred to a host computer. The RF channel data matrix was placed into a graphics processing unit (GPU) matrix within Matlab and multiplied by a beam-forming sparse matrix to get the beam-formed RF data (Hou et al. 2014a, Grondin et al. 2015). A 1D cross-correlation method (Luo and Konofagou 2010) was used to estimate the incremental axial displacement between two consecutive RF frames. HMI peak-to-peak displacement maps were calculated over each of the ten frames of HMI displacement maps by subtracting the minimum displacement from the maximum displacement on each pixel. When the processing is finished, another ten frames will be acquired for processing. The peak-to-peak HMI displacement map averaged over the first one s of treatment served as a reference map. The HMI lesion map was generated by subtracting the reference HMI image from the current HMI peak-to-peak displacement map, as displayed on the computer screen (figure 2).

Materials

In vitro canine liver specimens. Six in vitro canine liver specimens were used for this study as they are relatively homogeneous, allowing easy optical delineation of the lesions in gross pathology. Liver specimens were prepared and degassed for two hours before each experiment. After ablation, each liver specimen was carefully sectioned at the imaging plane under the guidance of B-mode imaging for gross pathology. The lesion area was delineated based on the color change in the tissue. The depth, width and area of the lesions measured on gross pathology were compared with HMI lesion mapping. We tested 0 dB, −1.5 dB, −3 dB and −6 dB thresholding. We then chose to set a −3 dB or 30% displacement decrease as the threshold to discriminate the ablated from unablated tissue as it yields the best correlation with gross pathology. The largest region closest to the geometric focus was identified as the lesion.
In vivo pancreatic tumor mouse experiment. The animal experiment protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Columbia University. The transgenic mouse model (K-\textsuperscript{rasLSL.G12D/}; p53\textsuperscript{R172H/+}; PdxCre (KPC)) (Olive and Tuveson 2006, Olive et al 2009) was used to develop a pancreatic tumor which pathophysiologically resembled a human pancreatic ductal adenocarcinoma. One KPC mouse was used for this study. The mouse lay supine under isoflurane anesthesia with its abdomen shaved and covered with ultrasound gel, with a degassed water tank on top to be coupled for ultrasound imaging. To precisely locate the pancreas, an 18.5 MHz diagnostic probe (L22-14v, Verasonics, Bothell, WA, USA) was used in the planning stage providing high-resolution B-mode images to locate and differentiate organs. By aligning the HMI imaging plane with the high-resolution B-mode images, the HMI images are spatially registered with the B-mode images. In the treatment monitoring stage, the center imaging probe of HMiFUS was replaced with a 104-element phased array (\(f_c = 7.8\) MHz, P12-5, ATL/Philips, Bothell, WA, USA) for higher resolution more adapted to small animals. The treatment power on the tumor was 6.4 W with 60 s duration.

The mouse was immediately sacrificed after the previously described procedure. Because gross pathology was incapable of distinguishing the ablated lesion from the pancreatic tumor, the whole pancreas along with the tumor was harvested for histological evaluation. The excised tissue was first fixed in 4% paraformaldehyde. After post-fixation processing, tissue was embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E). Bright field microscopy images were acquired and evaluated by a trained expert.

Figure 2. Flowchart of real-time HMI reconstruction algorithm.
Results

Real-time HMIgFUS ablation monitoring

The fast lesion mapping of HMIgFUS can stream the HMI displacement, HMI displacement overlaid on the B-mode and the HMI lesion map to the computer screen (figure 3) at an average frame rate of 2.4 Hz. In the HMI displacement map, positive displacement is towards the transducer and negative displacement is away from the transducer.

In vitro liver results

In order to prove the reproducibility of the technique, we have generated 13 lesions with HMIgFUS using different acoustic powers (6.4 W and 8.6 W) with different treatment durations varying from 90 s to 120 s. The lesions were detected and visualized at 2.4 Hz.

Figure 4 shows a representative case of HMIgFUS lesion monitoring over 90 s ablation. Yellow indicates the HMI peak-to-peak displacement amplitude increase (i.e., relative softening) and blue indicates the HMI peak-to-peak displacement amplitude decrease (i.e., relative stiffening). No lesioning was found by HMI until 50 s into the treatment when a dark blue spot was detected at the focal spot region (figure 4(a)) indicating tissue stiffening. The lesion was found to grow during ablation, which is also quantified in figure 4(d) showing that the lesion size increased after 50 s. When temperature rises above a certain threshold, liver tissue undergoes an irreversible stiffening change, which is caused by protein denaturation. According to established studies (Hill et al 1994, Hynynen 1996, Righetti et al 1999), 58–60 °C is the conventional ‘threshold’ for the formation of HIFU lesions in the liver. The temporal temperature profile (figure 4(e)) was obtained showing the temperature at the focal spot reaching the threshold of 60 °C at 30 s (denoted by the red line). Normalized HMI displacement within the focal region (Han et al 2015) was plotted against the temperature, clearly showing the displacement change with the temperature increase. A gross pathological cross section of the lesion is shown in figure 4(b) for comparison with the final HMI lesion map in figure 4(c).

Figure 5 is another representative case of 120 s HMIgFUS lesion monitoring. Lesioning was detected by HMI after 40 s of sonication with a decrease in displacement at the focal spot indicating tissue stiffening (figure 5(a)). Lesion growth during ablation is also quantified in figure 5(d) showing that the lesion size increased after 50 s. The temperature profile over time (figure 5(e)) showed that the temperature at the focal spot reached the 60 °C threshold at 30 s (denoted by the red line). Normalized HMI displacement within the focal region was also plotted against the temperature, clearly showing the displacement change with temperature. A gross pathological cross-section of the lesion is shown in figure 5(b) in comparison with the HMI final lesion map figure 5(c).

Statistical analysis was performed with linear regression in 13 HMIgFUS-induced lesions to compare the lesion dimension identified with HMI and gross pathology. The $R^2$ value from the linear regression analysis was respectively equal to 0.81 and 0.85 in depth and width. The linear regression performed in the lesion area gives a $R^2$ equal to 0.75 (figure 6).

Multiple-lesion results

In HIFU clinical applications, multiple-lesion ablations are often needed to treat the entire target region. When a few lesions occur close together, the lesions generated later start to merge into the prior ones. An example of a three-lesion HMIgFUS case is shown in figure 7. The three lesions are 3 mm apart at the same ablation power and duration starting from location 1.
and then move towards the right to locations 2 and 3 (figure 7(a)). The same lesion quantification protocol was used in each location. After combining lesion maps from the three locations, a final combined HMI lesion map was obtained, as depicted in figure 7(d).

**In vivo tumor results**

HMIgFUS lesion maps within the tumor area at the beginning \((t = 3 \text{s})\) and the end \((t = 59 \text{s})\) of the ablation are shown in figures 8(a) and (b). The pancreatic tumor was delineated based on the high-resolution B-mode images. In figure 8(a), the lesion map within the tumor was homogeneous and no lesion was indicated at the onset of the ablation. Figure 8(b) exhibits stiffening within the tumor after a 59 s ablation with a displacement reduction rate of 43.3%, suggesting lesion formation. The H&E staining results in figure 8(c) confirmed that the thermal lesion was generated in the tumor with apparent hemorrhage and tissue disruption.

**Discussion**

In the field of MRI and ultrasound imaging, numerous guidance techniques have been developed for the three stages of HIFU treatment: planning, monitoring and assessment. Although numerous methods have been developed to assist the three stages of HIFU treatment, real-time HIFU monitoring still remains a challenge. Real-time HIFU monitoring, especially lesion mapping, is essential during HIFU procedure as it can help avoid any over- or under-treatment. HMIgFUS is capable of performing HIFU monitoring based on the stiffness change of the tissue without interrupting treatment. Throughout this study, we developed a lesion quantification method using HMIgFUS, and investigated the feasibility of real-time lesion formation.
monitoring, which incorporated a GPU-based, fast beam-forming method. The lesion quantification method was validated through *in vitro* experiments in the liver and showed promising results *in vivo*.

In addition to lesion stiffening, softening was also detected at the focal spot when temperature is within the range of 40–60 °C before the lesion started to form (figure 4(a) at 30 s). This agreed with previous literature on the liver showing a slow, reversible shear modulus decrease under HIFU treatment before reaching the threshold of irreversible protein denaturation (Wu *et al* 2001). At the end of treatment, softening is also detected around the lesion boundary area in most cases indicating heat diffusion to the adjacent region. We found that heat diffusion after HIFU is terminated will not affect the lesion size significantly by comparing it with another lesion map acquired five min after ablation. According to the temperature profile obtained by the thermocouple, the temperature measured from the focal spot reverts to room temperature rapidly within one min after HIFU is terminated. A post-treatment HMI was performed five min after HIFU exposure showing that the lesion dimensions remain the same. Therefore, the lesion map at the end of HMIgFUS can represent the final lesion. Since the speed of sound change is filtered out from the displacement map (Maleke and Konofagou 2008), the effect of the speed of sound change due to temperature increase can also be excluded. Furthermore, the increase in attenuation can occur during thermal lesioning (Zderic *et al* 2004), resulting in increased absorption and therefore an increased radiation force within the stiffer lesioning area. However, it has been shown that the decrease in displacement amplitude occurs approximately after reaching 60 °C due to the combined effect of viscoelasticity changes

**Figure 4.** Example case of HMIgFUS lesion monitoring on 90 s ablation. Lesion developing overtime is shown in (a) with blue indicating the formation of the lesion. Gross pathology of the lesion (b) is shown along with the HMI lesion map at the end of the ablation (c). (d) HMI lesion size development overtime. (e) Temperature measurement from thermocouple. (f) HMI displacement change during the ablation.
and lesion growth overpowering the effect of attenuation (Hou et al 2015, Suomi et al 2016). The increased radiation force during ablation may generate an opposite lesion-to-background contrast by generating higher HMI displacement inside the lesion, which was not observed in this study. It is therefore concluded that the stiffening process is dominant over the change of absorption coefficient in HIFU ablation in the liver.

Despite our successful implementation on real-time HMIgFUS platforms, one limitation was that there was no absolute threshold of relative stiffness change to distinguish ablated liver tissue. However, the displacement change during and after treatment has shown enough

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**Figure 5.** Example case of HMIgFUS lesion monitoring on 120s ablation. Lesion developing overtime is shown in (a) with blue indicating the formation of the lesion. Gross pathology of the lesion (b) is shown along with the HMI lesion map at the end of the ablation (c). (d) HMI lesion size development overtime. (e) Temperature measurement from thermocouple. (f) HMI displacement change during the ablation.

**Figure 6.** Lesion dimension comparison between gross pathology and HMI lesion map in depth (left), width (middle) and area (right).
Figure 7. Multiple-lesion map using HMI in comparison with gross pathology. (a) HMI lesion map at lesions 1, 2 and 3. (b) Lesion gross pathology. (c) HMI lesion map at the end of ablation at lesions 1, 2 and 3. (d) Combined HMI lesion map.

Figure 8. HMIgFUS lesion formation monitoring in a mouse pancreatic tumor. HMIgFUS lesion map at (a) the beginning ($t = 3\, s$) and (b) the end ($t = 59\, s$) of the ablation with the tumor and adjacent organs marked. (c) H&E stained image of the pancreatic tumor after HIFU ablation show tissue disruption (red arrow), hemorrhaging (yellow arrow) and cell death (blue arrow). The scale bar represents 1 mm.
contrast to delineate the HIFU lesion. −3 dB or 30% decrease out of 0 dB, −1.5 dB and −6 dB showed the best agreement with the gross pathology. This can be improved by an optimization study, which can adapt the lesion threshold for each specific specimen. The lesion size was not quantifiable on H&E staining for two reasons: (1) it was difficult to register the imaging plane with the cutting plane in histology due to the harvest process; (2) soft tissue shrinks in the paraformaldehyde fixing process, which makes the lesion size smaller when compared with the actual lesion size in vivo. A registration method will be used in the future to register the orientation of the lesion with the help of surrounding organs. Another limitation of this study lies in the fact that only slow denaturation induced ablation was included in the study. However, previous work (Hou et al 2015) from our group has shown that HMIGFUS is robust under faster treatments such as boiling in monitoring the lesion formation in the presence of strong cavitation events with a good displacement contrast across the entire treatment window. The present study may have the potential to be applied on cavitation-induced HIFU treatment in the future.

As a final point, HMIGFUS combines HIFU and real-time elasticity imaging on the same device with the advantage of lesion formation monitoring without interfering with HIFU treatment. Future studies will consider the correlation between tissue structures and HMI characteristics to better understand tissue mechanical responses during HMIGFUS ablation.

Conclusion

A real-time (2.4 Hz) lesion detection and ablation monitoring method was developed using oscillatory radiation force induced displacement amplitude variations in real time. Lesion size monitoring was achieved in canine liver in vitro and initial in vivo feasibility was shown in a mouse pancreatic tumor model. Using this method, the HMIGFUS focal region and lesion formation were visualized in real time at a feedback rate of 2.4 Hz. By comparing the estimated lesion size against gross pathology, we have shown the feasibility of using HMIGFUS to monitor treatment and lesion formation without interruption in both the single-lesion and multiple-lesion configurations. The study presented here with validated that HMIGFUS could map lesion formation during HIFU treatment and was capable of real-time HIFU monitoring.

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