Comparative study of temperature measurements in *ex vivo* swine muscle and a tissue-mimicking material during high intensity focused ultrasound exposures

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Comparative study of temperature measurements in \textit{ex vivo} swine muscle and a tissue-mimicking material during high intensity focused ultrasound exposures

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Abstract

Tissue-mimicking materials (TMMs) can provide a convenient, stable, and reproducible means for testing high intensity focused ultrasound (HIFU) devices. When TMMs containing thermal sensors are used to measure ultrasound-induced temperature rise, it is important that measurement results reasonably represent those that occur in biological tissue. Therefore the aim of this paper is to compare the thermal behavior of the TMM under HIFU exposure to that of \textit{ex vivo} tissue. This was accomplished using both a previously developed TMM and fresh \textit{ex vivo} swine muscle that were instrumented with bare 50 μm thin wire thermocouples. HIFU at 825 kHz was focused at the thermocouple junction. 30 s exposures of increasing peak negative pressure (1 to 5 MPa) were applied and the temperature profile during and after sonication was recorded. B-mode imaging was used to monitor bubble activity during sonication. If bubble formation was noted during the sonication, the sonication was repeated at the same pressure levels two more times at 20 min intervals. Temperature traces obtained at various pressure levels demonstrated similar types of heating profiles in both the tissue and TMM, the exact nature of which depended on whether bubbles formed during the HIFU exposure. The onset of bubble activity occurred at lower ultrasonic pressures in the TMM, but the basic temperature rise features due to HIFU exposure were essentially the same for both materials.

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

Introduction

With the emergence of high intensity therapeutic ultrasound as a viable medical treatment for a wide range of cancers as well as benign masses (ter Haar 2007), the development of standard exposimetry techniques is necessary. However, due to the high pressures and high temperatures generated during high intensity focused ultrasound (HIFU) exposures, \textit{in vitro} or...
monitoring techniques are often challenging to implement. Along with free-field power and intensity characterization, device pre-clinical testing should include the measurement of temperature in a well-characterized tissue-mimicking material (TMM) (Shaw et al. 1999, IEC 2010) or in ex vivo tissue to demonstrate that predictable temperature distributions can be produced. Both materials have advantages for pre-clinical performance and safety testing. TMMs can be made both reproducible and reusable; ex vivo tissue, if properly handled, will closely match the inhomogeneous nature of tissue in vivo. However, both need to be evaluated under exposure conditions that give rise to the formation of bubbles, because during HIFU procedures bubble creation can produce focal temperatures that are difficult to predict (Clarke and ter Haar 1997, Canney et al. 2010).

Several HIFU pre-clinical investigations have been performed using TMMs embedded with thermocouples (Holt and Roy 2001, Chen et al. 2009, Farny et al. 2009, Coussios et al. 2007). In these particular studies the TMMs were PVA-, agar- or gelatin-based, and the thermocouples were bare wire, Type-E (chromel–constantan) having a diameter of 0.13 mm. B-mode imaging or cavitation sensors also were employed to detect the presence of ultrasound-generated bubbles. Such bubble detection techniques have also been used without embedded thermocouples to explore the role of bubble formation and collapse on HIFU lesion production (McLaughlan et al. 2010, Zhang et al. 2009). A few studies are available in which thermocouples have been used in ex vivo animal tissue to record the temperature rise associated with HIFU exposure (Hynynen (1991), canine thigh muscle; Bailey et al. (2001), excised bovine liver; Morris et al. (2008), bovine liver; McLaughlan et al. (2010), bovine liver). However, in none of these studies were ex vivo and TMM results directly compared.

The aim of this paper is to compare the thermal behavior of a HIFU TMM under high intensity ultrasound exposure to that of ex vivo tissue as determined by thermocouple measurements. Thermocouple-based temperature measurements are evaluated using both ex vivo swine muscle and a TMM previously developed at the FDA specifically for HIFU pre-clinical testing. Ultrasound B-mode imaging was used to monitor the onset of bubble creation and aid in assessing the effect of bubble presence on the thermocouple response. Although passive cavitation detection has been used to detect bubbles (e.g. McLaughlan et al. 2010), the main thrust of this paper is temperature measurements during HIFU exposure, and the hyperechogenicity observed in the B-mode images due to the presence of bubbles was found to correlate well with anomalous changes in the thermocouple output, as demonstrated in the results for both TMMs and swine muscle. Temperature trace patterns associated with both pre- and post-bubble activity are described, and bubble-formation onset pressures are identified. By applying the same HIFU exposure conditions to both the TMM and tissue, it was possible to obtain a direct comparison of how the TMM behaved relative to the ex vivo tissue. Further, using both TMM and ex vivo tissue samples permitted a comparison of (1) how the occurrence or presence of bubbles can affect temperature measurements using thin wire thermocouples, (2) onset pressures for thermally significant bubble formation, and (3) how repeatable the temperature measurements are at pressure levels greater than the onset pressure. By ‘thermally significant’, a term taken from Hynynen (1991), we mean that the region heated due to bubble action is large enough to have clinical relevance for thermal therapy.

Another distinctive feature of the present study lies in how the actual end of sonication (EOS) temperatures were determined, given the thermocouple’s expected viscous heating artifact (Morris et al. 2008) and possible very local cavitation effects due to the presence of the thermocouple. An extrapolation approach similar to that of Parker (1983) was used, in which a portion of the thermocouple’s cooling curve not affected by the viscous heating artifact was extrapolated back to the time of shut-off. However, unlike Parker (1983), who used a theoretical cooling expression requiring knowledge of the thermal diffusivity and intensity
distribution, we employed a straightforward mathematical fit to the temperature data as will be explained.

With regard to the size of thermocouple used, guidelines have been given to avoid perturbing the ultrasound field. Fry and Fry (1954) recommended that the probe size be less than $\lambda/20$, where $\lambda$ is the ultrasound wavelength. Hynynen and Edwards (1989) proposed that thermocouples with diameters less than $\sqrt{\lambda}/5$ have an insignificant effect of the temperature distribution due to ultrasound beam perturbation. However, the viscous heating artifact and local cavitation effects can still be appreciable even with these small probes, and so the relationship between thermocouple size, beam size, and the temporal window during which viscous heating is significant is discussed.

Materials and methods

Experimental system

The experimental system (figure 1) included a 10 cm diameter HIFU transducer (King Acoustic Technologies, Washington, DC) with 10 cm focal length that was driven at its fundamental frequency of 825 kHz. The ultrasonic power was measured using a radiation force balance system and was varied from 5 to 30 W. Hydrophone scanning (Model 500B, ONDA Corp., Sunnyvale, CA) was used to determine the –6 dB focal beam dimensions of the transducer (2.7 mm lateral and 17 mm axial). The driving electronics consisted of a function generator (Wavetek 81, Fluke Corp., Everett, WA) and power amplifier (ENI 2100L or ENI A-300,
Figure 2. TMM mold with affixed thermocouple before (left) and after (right) pouring the TMM.

Table 1. Acoustic parameters used for modeling the HIFU pressure in the TMM and swine muscle (standard deviations and ranges are provided where available).

<table>
<thead>
<tr>
<th>Acoustic modeling parameters</th>
<th>TMM</th>
<th>Swine muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of sound (m s(^{-1}))</td>
<td>1534 ± 16</td>
<td>1529–1629</td>
</tr>
<tr>
<td>Density (kg m(^{-3}))</td>
<td>1040</td>
<td>1050</td>
</tr>
<tr>
<td>Attenuation at 1 MHz (dB cm(^{-1}))</td>
<td>0.71 ± 0.05</td>
<td>0.48–1.00</td>
</tr>
<tr>
<td>Power of attenuation versus frequency curve</td>
<td>0.86 ± 0.03</td>
<td>1</td>
</tr>
<tr>
<td>Nonlinearity parameter B/A</td>
<td>8.2</td>
<td>5.5–7.6</td>
</tr>
</tbody>
</table>

Rochester, NY). A 50 dB dual-directional coupler (Amplifier Research, Model DC2000, Souderton, PA), two power sensors (Model 8482A, Agilent Technologies, Palo Alto, CA), and a power meter (Model E4419B, Agilent Technologies, Palo Alto, CA) were placed between the amplifier and transducer to monitor the forward and reversed electrical power to the transducer. Sonications were performed under MATLAB control (Mathworks, Inc., Natick, MA). The presence of bubbles was monitored with a Siemens Antares diagnostic imaging system (Siemens Medical Solutions, Malvern, PA). Imaging was performed at 5.33 MHz using the Model VF7-3 linear array.

**TMM and thermocouple placement**

A hydrogel-based TMM was used that had acoustic and thermal properties similar to that of human soft tissue (King et al 2011). The acoustic attenuation, speed of sound, nonlinearity parameter B/A, and thermal diffusivity and conductivity were measured at room temperature (22 ± 2 °C) and found to approximate published values for soft tissue at physiologic temperatures (table 1).

A 5 cm deep cylindrical mold having an inner diameter of 8 cm was constructed with an opening for the imaging transducer (figure 2). A 50 μm diameter Type E (chromel–constantan) bare wire thermocouple (Omega Engineering Inc., Stamford, CT) was affixed through the center of the mold. The TMM mold with the thermocouple was then cleaned.
Comparative study of temperature measurements in ex vivo tissue and TMM during HIFU exposures

by boiling in distilled water with added surfactant for 20 min to minimize the presence of bubble-forming nuclei. Once the TMM was prepared, it was immediately poured into the mold with the thermocouple and allowed to set. During use, the thermocouple was positioned at the HIFU transducer focus by maximizing the temperature indication under a low intensity exposure. The temperature measured using the thermocouple during the HIFU sonication was recorded via a computer controlled acquisition system (OMB-DAQ-3000, Omega Engineering Inc., Stamford, CT). The sampling rate for this system is 5 Hz. The measurement uncertainty for the temperature rise is ±0.3 °C.

Muscle tissue collection and thermocouple placement

Seven muscle tissue samples were collected from five domestic swine (mean weight: 88 ± 28 kg, range: 58–114 kg) following completion of unrelated studies and euthanasia that were performed under research protocols approved by the Institutional Animal Care and Use Committee. The animals had been maintained under general anesthesia with isoflurane (Isoflo, Abbott Animal Health, North Chicago, IL), an anesthetic used in other ultrasound bubble studies involving animals (Rabkin et al. 2005). No unique effects relevant to ultrasound exposure due to uptake of isoflurane along with other respiration gases in tissue have been reported to the authors’ knowledge. Immediately following euthanasia by administration of Euthasol (Virbac, Inc., Fort Worth, TX), the longissimus dorsi muscles of the back were resected and cut into 9–10 cm long segments. The dorsal and ventral fascia were sliced smoothly from the body of the muscle and the segments trimmed to fit into the tissue holder. The tissue holder was a modified version of the TMM mold. The holder had an internal diameter of 8 cm, a depth of 5 cm, and a side opening for insertion of the imaging transducer. Two 1.5 mm holes were drilled in the mid-plane of the cylinder on diametrically opposed sides for thermocouple insertion. One end of the thermocouple wire was soldered adjacent to one of the holes such that the junction of the wires would be at the mid-point of the cylinder within the tissue when drawn taut across the holder. The other end was left free for insertion through the muscle.

After the muscle was trimmed, all further manipulation of the specimen was conducted in a container of degassed normal saline (0.9% NaCl) to prevent introduction of air into the muscle. The muscle specimen was placed in the submerged holder. An 18 g, 15 cm long Chiba needle (Cook Medical, Bloomington, IN), which has a beveled tip and a solid obturator with matching beveled end, was flushed under saline to remove air from the lumen. The needle and obturator were inserted through one side hole in the holder, through the specimen and through the exit hole on the opposite side. The obturator was withdrawn and a loop of wire (36 μm diameter) was advanced through the needle. The free end of the 50 μm diameter fine wire thermocouple was bent and hooked on the wire loop and then pulled through the needle. The needle was withdrawn from the specimen and the wire was pulled taut. The entrance and exit points of the wire at the edge of the muscle were inspected to ensure that no loops of wire were present. The open ends of the holder were covered with 25 μm thick Mylar film secured by an O-ring while submerged under degassed normal saline. Figure 3 shows the holder before and after placement of the tissue. As with the TMM, the Omega DAQ system was used to record the temperature rise due to HIFU sonication focused at the junction of the thermocouple wire. All HIFU exposures were conducted within 3 h of tissue resection.

Experimental protocol

Experiments were performed at room temperature in a large tank filled with degassed, deionized water (22 ± 2 °C). Swine muscle or TMM was sonicated for 30 s starting at the
lowest pressure level (sonication level 1) and the temperature rise was recorded before, during, and after sonication. The increasing pressure levels corresponded to a range of focal peak negative pressures that varied approximately from 1 to 5 MPa (see table 2). The determination of the simulated values of the focal pressures within either the tissue or the TMM is described in the next section. Before HIFU sonication, the imaging transducer was positioned to image the focal plane so that the imaging beam, approximately 2–3 mm in diameter at its focus, encompassed the HIFU focus and thermocouple junction. Ultrasound images were taken during and after sonication. If bubble formation was not detected in the temperature trace (via an abnormal increase or decrease) or observed in the ultrasound image (via scattering pattern), sonication was continued at the next higher pressure amplitude after the temperature had returned to baseline. If bubble formation was seen, then the sonication was repeated at the same pressure level after a 20 min wait to allow the sample to cool back to ambient water temperature to within ± 2 °C. This procedure was performed twice after the initial sonication, giving a total of three sonications for cases of observed HIFU-induced bubble activity. At the 20 min point, no evidence of bubbles was seen in the B-mode images. Determining the cause of bubble formation was not a goal of this study, but it is noted that no recorded temperatures exceeded 95 °C.

**Determination of focal pressure and intensity**

In order to obtain a more accurate assessment of the actual *in situ* acoustic pressure at the focus within the TMM and swine muscle, simulations from a two-layer nonlinear propagation model based on the KZK equation were performed using the measured acoustic power for the 0.825 MHz transducer (Soneson 2008). Hydrophone measurements were carried out to confirm the KZK calculations. The measurements were made at low power to avoid hydrophone damage, and the differences between simulation and measured pressure values were within about 15%. The acoustic parameters used for the simulations for the TMM and swine muscle are given in table 1. The average attenuation of 0.71 dB cm⁻¹ MHz⁻⁰.₃₆ from 2 to 8 MHz, where *f* is in MHz, as well as the average sound speed of 1534 m s⁻¹ and the tissue-like image quality, indicate the usefulness of the TMM for ultrasound imaging applications. These properties along with a nonlinearity parameter *B/A* of 8.2, thermal conductivity of 0.58 W m⁻¹ °C⁻¹, diffusivity of 0.15 mm² s⁻¹, and the ability to withstand temperatures at least to 95 °C make this TMM appropriate for HIFU applications.
Comparative study of temperature measurements in ex vivo tissue and TMM during HIFU exposures

**Figure 4.** Example simulation results for swine muscle from a two-layer nonlinear propagation model based on the KZK equation. $p_+$ and $p_-$ are the peak positive and negative pressures, respectively.

**Table 2.** *In situ* pressure values obtained from the simulation for the TMM and swine muscle.

<table>
<thead>
<tr>
<th>Sonication level</th>
<th>TMM</th>
<th>Swine muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p_-$ (MPa)</td>
<td>$I_{SPTA}$ (W cm$^{-2}$)</td>
</tr>
<tr>
<td>1</td>
<td>0.9</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>1.6</td>
<td>101</td>
</tr>
<tr>
<td>3</td>
<td>2.1</td>
<td>181</td>
</tr>
<tr>
<td>4</td>
<td>2.7</td>
<td>314</td>
</tr>
<tr>
<td>5</td>
<td>3.3</td>
<td>518</td>
</tr>
<tr>
<td>6</td>
<td>3.8</td>
<td>738</td>
</tr>
<tr>
<td>7</td>
<td>4.7</td>
<td>1266</td>
</tr>
</tbody>
</table>

The parameter values for the TMM were measured in our laboratory. The range of values shown in table 1 for swine muscle are taken from ICRU Report 61 (1998); for the simulations the mid-point values were used. The simulations yielded the axial pressure and intensity waveforms, as illustrated in figure 4 for the swine muscle.

Table 2 contains the range of values used for $p_-$, and the spatial peak temporal average intensity, $I_{SPTA}$. All pressure and intensity values shown in table 2 are *in situ* values.

**Temperature analysis**

The temperature measured using the thermocouple at the EOS may be different than the actual temperature were the thermocouple not present. This difference may be due to viscous heating of the thermocouple, cavitation yielding enhanced or diminished heating at and due to the presence of the thermocouple, and other thermocouple artifacts such as thermal conduction due to the metal of the thermocouple or distortion of the ultrasound beam due to the wire. However, for the thermocouple size used in this work, neither thermal conduction nor distortion of the ultrasound beam would be significant (Morris et al 2008, Dickinson 1985). In order to better determine the actual EOS temperature given these measurement artifacts, the thermal decay curve following the EOS was extrapolated back to the ultrasound ‘off’ time. Parker (1983) described a back extrapolation technique based on a model of the temperature decay for obtaining the actual EOS temperature in connection with measuring the ultrasonic absorption.
Table 3. Comparison of results using various mathematical fits on modeled temperature data. The fits are performed in the range 2–12 s after the EOS. The reference temperature of 49.15 °C was obtained using Hariharan et al (2007).

<table>
<thead>
<tr>
<th>Fit</th>
<th>Reference EOS value equation</th>
<th>EOS T</th>
<th>% diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cubic polynomial</td>
<td>( y = y_0 + ax + bx^2 + cx^3 )</td>
<td>49.31</td>
<td>0.3%</td>
</tr>
<tr>
<td>Single, three-parameter exponential decay</td>
<td>( y = y_0 + ae^{-bx} )</td>
<td>49.52</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hyperbolic decay, two parameters</td>
<td>( y = ab/(b+x) )</td>
<td>50.03</td>
<td>1.8%</td>
</tr>
<tr>
<td>Single rectangular hyperbola II, three parameters</td>
<td>( y = ax/(b+x) + cx )</td>
<td>49.55</td>
<td>0.8%</td>
</tr>
<tr>
<td>Double rectangular hyperbola, four parameters</td>
<td>( y = ax/(b+x) + cx/(d+x) )</td>
<td>51.20</td>
<td>4.2%</td>
</tr>
<tr>
<td>Modified hyperbola II</td>
<td>( y = x/(a+b) )</td>
<td>51.20</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Figure 5. Example of a temperature rise curve at sonication level 3 with the cubic fit and extrapolated EOS temperature overlaid.

We employed an alternative approach for the extrapolation, by best-fitting the experimental temperature decay data from 2 to 12 s after the ultrasound exposure ceased, to ensure that the viscous and/or cavitation effects introduced by the thermocouple sensor were avoided. Specifically, a cubic fit was performed on these 10 s sections of the temperature traces. A cubic fit was employed because this form gave the best estimate of all analytic functions examined for the EOS temperature rise based on back extrapolation of temperature decay curves theoretically derived using Hariharan et al (2007), whose model was validated against the experimental data from other researchers (Wu and Du 1990, Huang et al 2004, Meaney et al 1998). A comparison of the various mathematical fits is shown in table 3. Using different time windows (10 and 20 s windows starting at 0.2, 1, 2, 5, 7, and 10 s after EOS) produced very little variation in the extrapolated EOS temperature. However, considering the findings of Morris et al (2008) that for 200 μm diameter thermocouples, viscous effects could still be significant up to 5 s after cessation of ultrasound exposure, a justification for our back extrapolation protocol and the 2 s starting time is provided in the discussion. This theoretical analysis, coupled with the just mentioned independence of the EOS temperature with window starting time, demonstrate that 2 s is a conservative starting time given the size of the thermocouples we employed (50 μm).

Figure 5 shows an overlay of the fit curve on an example experimental temperature trace \( R^2 = 0.999 \). No abrupt changes indicative of bubble formation are present. Effects due to very
local thermocouple perturbation decay quickly after the EOS, leaving a temperature decay curve indicative of a millimeter (focal dimensions) rather than micrometer (thermocouple dimensions) heated volume. Further analysis is presented in the discussion.

Results

**TMM results**

Six TMMs were sonicated according to the protocol described. Figure 6 shows examples of various temperature rise curves at non-bubble-inducing and bubble-inducing pressure levels in the TMMs. The black dots indicate the extrapolated EOS temperature rise. Figure 6(a) is an example of temperature rise curves in one TMM sample that do not contain evidence of induced bubble activation. That is, the temperature traces are smooth and monotonically increasing during the exposure. An artifact indicative of viscous heating (Morris et al 2008) is present in the level 2 trace, as evidenced by the difference between the final thermocouple value and the extrapolated EOS temperature rise in the absence of perceived bubble formation. A similar but smaller temperature difference was seen at level 1. This effect was linear with relative intensity as would be expected for a viscous heating artifact.

Figure 6(b) is an example of induced bubble formation on the first run, while the next two runs yielded expected smooth temperature traces. However, the extrapolated EOS temperatures for all three runs are nearly the same, indicating that bubble formation in run 1 was a very local (not thermally significant) event that did not affect the absorption of energy in most of the
focal region within the TMM. That is, if significant non-localized bubble formation had led to enhanced heating as seen at the EOS in run 1, then the cooling curve would have decayed much more slowly due to the thermocouple junction being influenced by elevated temperatures away from the junction. The rapid decay observed means that only a region immediately around the junction experienced enhanced heating.

Figure 6(c) also contains an example of induced bubble formation in only the first run; however the extrapolated EOS temperature is noticeably higher than the extrapolated EOS temperatures for the following two runs, which yielded smooth, monotonically increasing temperature traces during sonication as shown in figure 6(a) with no evidence of thermally significant bubble formation. This is an indication of bubble-enhanced heating of a larger region surrounding the thermocouple junction compared to run 1 shown in figure 6(b). This phenomenon could be explained by a combination of increased absorption and inertial bubble collapse causing local high temperature rise as seen by other researchers (Coussios et al 2007). The sharp spike occurring in the run 1 trace of figure 6(c) does correspond to a very local and thermally insignificant heating event at or very near the thermocouple junction. In figure 6(d), run 1 shows obvious decreased heating while runs 2 and 3 show bubble-induced changes in the temperature profile.

Figures 7(a) and (b) contain example B-mode images associated with thermally insignificant and significant bubble formation and heating, respectively. The frame rate was 30 frames per second, and images were stored every few seconds. Figure 7(a), corresponding to figure 6(b), run 1, contains no hyperechogenic regions (bright spots), even though the temperature trace displays an abrupt and dramatic rise and fall at the beginning and end of sonication. The image at 6 s into sonication shows a funnel pattern, narrowest near the location of the HIFU focus, which is attributable to interference noise likely due to electrical saturation in the receiving electronics caused by large amplitude scattering of the HIFU beam into the imaging transducer (Wu et al 2008).

Figure 7(b), corresponding to figure 6(d), run 1, shows a marked hyperechogenic spot, as illustrated in the image at 14 s, which persists after the sonication has ended. This spot is indicative of bubble cloud formation, leading to the beam blockage and decreased heating as described above for figure 6(d), run 1.

Figure 8 contains images similar to those in figure 7(b) at five time points on the temperature trace shown in the figure. Hyperechogenic regions are highlighted by the circled regions at time points 3–5. Acoustic shadowing can be seen at time point 4.

The temperature traces and images shown in figures 6–8 can be grouped into two main categories: (1) no or insignificant bubble formation (essentially normal temperature curves and no hyperechoic regions seen in the ultrasound images, but sometimes interference (funnel) patterns observed); and (2) thermally significant bubble formation (temperature curves showed enhanced or decreased heating and hyperechoic regions formed on the ultrasound image during sonication).

The extrapolated EOS temperature rise values for each TMM are plotted in figure 9. If bubble activation occurred at a particular level, then the point on the plot is an average of the three sonications. Error bars representing the standard deviations for these averaged values are indicated in the figure.

Table 4 gives the ranges for the onset pressures of thermally significant bubble formation in the TMMs based on observed anomalies in the temperature trace with corresponding hyperechoic region formation in the B-mode images. For example, regarding the first row in the table, in this TMM sample bubbles were not detected at level 1 but were at level 2, so the \( p \) value fell somewhere between 0.9 and 1.6 MPa. Based on the upper level values of each
Comparative study of temperature measurements in ex vivo tissue and TMM during HIFU exposures

Figure 7. (a) Example of thermally insignificant bubble formation corresponding to the run 1 temperature trace shown in figure 6(b). (b) Example of thermally significant bubble formation corresponding to the run 1 temperature trace shown in figure 6(d).

Table 4. Ranges for the onset of HIFU-induced bubble formation in the TMMs.

<table>
<thead>
<tr>
<th>Sonication level</th>
<th># of samples</th>
<th>( p_0 ) (MPa)</th>
<th>( I_{SPTA} ) (W cm(^{-2}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>1</td>
<td>0.9–1.6</td>
<td>25–101</td>
</tr>
<tr>
<td>2–3</td>
<td>4</td>
<td>1.6–2.1</td>
<td>101–181</td>
</tr>
<tr>
<td>3–4</td>
<td>1</td>
<td>2.1–2.7</td>
<td>181–314</td>
</tr>
</tbody>
</table>

sonication level range for each TMM sample, the estimated average onset pressure was 2.1 ± 0.3 MPa.

Swine muscle results

Seven swine muscle samples were sonicated according to the protocol described. As with the TMMs, bubble formation was indicated by anomalies in the temperature traces with corresponding hyperechoic region formation in the B-mode images. Analogous to figure 6, figure 10 shows an example of various temperature rise curves at non-bubble-inducing and bubble-inducing pressure levels in the swine muscle samples. The black dots indicate
Figure 8. Example of a sonication in the TMM. The numbers on the graph correspond to the numbered ultrasound images. Evidence of bubble-enhanced heating in the temperature trace is shown between points 1 and 2; evidence of shielding is shown between points 2 and 4. The black dot at point 4 represents the extrapolated EOS temperature rise. White ROIs identify hyperechogenic regions.

Figure 9. Extrapolated EOS temperature rise values for the six TMMs. Error bars represent standard deviations for the points that are the average of three sonications.
the extrapolated EOS temperature. Figure 10(a) shows a range of smooth, monotonically increasing temperature rise curves during sonication (i.e. traces that did not have evidence of bubble formation) in one tissue sample. When bubbles were induced, as evidenced by anomalies in the temperature traces, a number of different trace features were observed, as seen in figures 10(b)–(d). The initial steep rise seen in several of the traces (e.g. 10(c), run 1) is indicative of bubble-enhanced heating at the thermocouple junction, although a viscous heating component likely contributes also. One possible explanation for the shapes of the run 1 curves shown in figures 10(b) and (c) is an initial enhancement, followed by shielding as more bubbles form. For these 30 s sonications shown in figures 10(b)–(d) the three extrapolated EOS temperatures were similar (to within about ±5 °C for each level) even though the shape of the curves varied appreciably.

For the pig muscle samples, again the temperature traces can be grouped into two categories: (1) no or insignificant bubble formation (normal temperature curves and no changes in the ultrasound images as can be seen in figure 11); and (2) thermally significant bubble formation (temperature curves showed enhanced or decreased heating and hyperechoic regions formed on the ultrasound image during sonication). Figure 12 shows an example of category (2), in which the temperature trace contains evidence of bubble-enhanced heating (time point 1) as well as decreased heating (time point 3). In the corresponding ultrasound images the formation of a bubble cloud is noted by the circled regions.
Figure 11. Example of non-bubble-inducing exposure in swine muscle: normal temperature curves and no changes seen in the ultrasound images. The black dots represent extrapolated EOS temperature rises. The numbers on the graph correspond to the numbered ultrasound images.

Table 5. Ranges for onset of HIFU-induced bubble formation in the swine muscle samples.

<table>
<thead>
<tr>
<th>Sonication level</th>
<th># of samples</th>
<th>$p_-$ (MPa)</th>
<th>$I_{SPTA}$ (W cm$^{-2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–4</td>
<td>1</td>
<td>2.2–2.8</td>
<td>178–307</td>
</tr>
<tr>
<td>4–5</td>
<td>2</td>
<td>2.8–3.5</td>
<td>307–503</td>
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<tr>
<td>5–6</td>
<td>3</td>
<td>3.5–4.0</td>
<td>503–712</td>
</tr>
<tr>
<td>6–7</td>
<td>1</td>
<td>4.0–5.0</td>
<td>712–1202</td>
</tr>
</tbody>
</table>

Analogous to figure 9, the extrapolated EOS temperature rise values for each swine muscle sample at both non-bubble-inducing and bubble-inducing pressures are plotted in figure 13. These two figures are compared in the discussion.

Table 5 gives the ranges for the onset pressures and intensities of thermally significant bubble formation in the swine muscle. The estimated onset pressure, again based on the upper level values of the sonication level ranges, was 3.8 ± 0.7 MPa. As expected, visual inspection of the muscle after exposure showed lesion formation at the location of the HIFU focus, e.g. see figure 14(a), which shows evidence of ‘tadpole’ formation (Bailey et al 2001) due to the bubbles seen in 14(b).

Discussion

**TMM versus ex vivo tissue**

TMMs are intended primarily as stable and reproducible means for pre-clinical testing and not as an exact match to tissue for biological or clinical studies. Nonetheless, their behavior
Comparative study of temperature measurements in ex vivo tissue and TMM during HIFU exposures

Figure 12. Example of thermally significant bubble formation in swine muscle. The numbers on the graph correspond to the numbered ultrasound images, which contain white ROIs identifying hyperechogenic regions. Evidence is shown in the temperature trace of bubble-enhanced heating during the initial rise indicated by point 1; evidence of shielding is shown between points 2 and 3. The black dot at point 3 represents the extrapolated EOS temperature rise.

Figure 13. Extrapolated EOS temperature rise values for the seven swine muscle samples at non-bubble-inducing and bubble-inducing sonication pressures.
during HIFU exposures, along with their acoustic and thermal properties, should reasonably represent that of tissue. The time–temperature characteristics recorded by the thermocouples were similar for both the TMM and the ex vivo muscle (cf figures 6–8 with 10–12), although the onset pressure levels for thermally significant bubble formation in the TMM were lower. If the HIFU exposures in muscle had been performed at 37 °C, rather than at 22 °C room temperature, as is typically done for tissue studies, then the onset pressure levels likely would have been closer to each other because at higher absolute temperatures, bubbles form at lower p* values.

A relatively low HIFU frequency (<1 MHz) was chosen for this study to increase the likelihood of bubble formation and its attendant effects at a given pressure level. Before bubbles formed the temperature traces were as expected, the only artifact noted being viscous heating as described in Morris et al (2008). When evidence of thermally significant bubble formation was seen in the thermocouple measurements, the ultrasound image for both the TMM and the ex vivo tissue always contained the corresponding feature of a hyperechoic region. This region dissipated during the 20 min between repeat sonications. Conversely, we never observed a hyperechoic region when there were no thermally significant bubble formation features seen in the thermocouple output. The variable results observed after bubbles formed in the HIFU TMM used in this study support results seen in other TMMs embedded with thermocouples (Holt and Roy 2001, Chen et al 2009, Farny et al 2009, Coussios et al 2007). Our measurements also demonstrate this same difficulty for ex vivo tissue regarding predicting the actual EOS temperature after bubble formation has occurred.

The extrapolated EOS temperature rise values shown in figures 9 and 13 show greater variability for the ex vivo muscle than for the TMM. To quantify this observation, the per cent coefficient of variation for each material was computed, first for runs in which no bubbles were observed, and then when they were observed. The results are: TMM (no bubbles)—9%; ex vivo tissue (no bubbles)—26%; TMM (bubbles)—17%; ex vivo tissue (bubbles)—24%. It is noted that not only did the ex vivo muscle display greater variability than the TMM, but that variability was great whether or not bubbles were induced, likely due to the inherent
Comparative study of temperature measurements in *ex vivo* tissue and TMM during HIFU exposures 17

inhomogeneity of tissue. The flattening or decrease in temperature rise at the higher sonication levels shown in both figures 9 and 13 reflect the blocking effect of the bubbles.

**EOS temperature via back extrapolation**

In the materials and methods section, a back extrapolation method was described for determining the EOS temperature, based on applying a cubic fit to 10 s of the cooling curve beginning 2 s after the EOS. As explained in the following analysis, the time delay used as the starting point is not significant, and 2 s was chosen as a convenient value. We assume that, for a theoretical model of the temperature decay due to thermocouple-induced viscous heating or bubble formation, these thermal sources occur close to the thermocouple. This is a necessary assumption because only local thermocouple perturbations can be corrected via the back extrapolation technique. For this situation a roughly spherically circular thermal source is an adequate model. For such a source, the time it takes for the temperature to decay to 20% of its steady-state value after the source has been turned off is approximately proportional to the square of the volume’s linear dimension. Assuming the thermal constants of soft tissue (or our TMM), the approximate time in seconds to decay to 20% of the final temperature rise is $175d^2$, where $d$ is the diameter of the heated volume in cm (Nyborg 1977, Carslaw and Jaeger 1959 p 257). This is a worst case result, because the thermal conductivity of the chromel and constantan comprising the thermocouple wires is 32 times that of tissue, and a higher conductivity would speed up the return to baseline temperature within the thermocouple. For a sphere whose diameter is the size of the thermocouple junction (0.005–0.01 cm diameter) this decay time is less than 0.2 s, the smallest value used for the extrapolation window starting point in our analysis of the back extrapolation approach.

This time for the temperature changes associated with the thermocouple to decay can be contrasted with the decay curve for the volume of tissue heated within the ultrasound focus by using the Bacon and Shaw (1993) formulation for the temperature at the focus of an ultrasound beam. By such calculation the time to decay to 20% of the temperature rise after a 30 s exposure, for an assumed ultrasound beam diameter of 2.7 mm in tissue, is $>100$ s. We thus see that the temperature decay, even with only a 0.2 s delay after the end of exposure, is almost entirely indicative of that due to tissue absorption within the focal volume and can be used to extrapolate the EOS temperature. Using a time window beginning at 2 s after ultrasound shut-off gives a bigger margin of safety that the thermocouple effects are not biasing the results. Further, the back extrapolation technique weights the temperature correction with data at greater times over which the viscous (or local bubble) artifacts have subsided. That is, temperature errors due to artifacts occurring at time points close to the EOS are mitigated by back extrapolation, as long as the time record to be extrapolated mainly comprises temperatures that represent the actual cooling of the tissue surrounding the thermocouple junction.

**Summary**

The temperature rise during HIFU sonication was investigated in both *ex vivo* swine muscle and a HIFU TMM that was designed to mimic soft tissue acoustically and thermally. In these essentially side-by-side comparisons, temperature traces obtained at various pressure levels demonstrated similar types of heating profiles in both the tissue and the TMM, the exact nature of which depended on whether bubbles formed during the HIFU exposure. Therefore, in both, HIFU-induced bubble effects must be considered. The onset of bubble activity occurred at lower ultrasonic pressures in the TMM than in the *ex vivo* swine muscle, although if the *ex vivo* exposures had been conducted at body rather than at room temperature, the onset pressures
likely would have been lower. Once bubbles form, regardless of their origin, care must be taken in interpreting the results due to the possibility of both enhanced heating and shielding. The mechanism of bubble formation (e.g., cavitation and/or boiling) was not a goal of this study, although no absolute temperatures greater than 95 °C were recorded. An alternative method was presented for back extrapolation of the temperature decay curve to determine the actual EOS temperature in the presence of thermocouple artifacts. In this study, thermally significant bubble formation seen in the thermocouple measurements always correlated with hyperechogenicity in the B-mode images.

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