

● *Original Contribution*

## THE TEMPERATURE DEPENDENCE OF ULTRASOUND-STIMULATED ACOUSTIC EMISSION

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(Received 26 June 2001; in final form 17 December 2001)

**Abstract**—Given the high variability of tissue properties during sonication, temperature monitoring is one of the most crucial components for accurate thermal treatment of tissues with focused ultrasound and other thermotherapy devices. Recently, the method of ultrasound-stimulated acoustic emission (USAE) has been introduced as a potential method for measurements of mechanical properties of tissues. In this paper, the dependence of USAE on tissue temperature is determined. Because USAE depends on the acoustic and mechanical properties, both of which vary with temperature, it is hypothesized that the USAE signal is also temperature-dependent and in such a way that it can be used to guide thermal therapy. In a series of experiments, *ex vivo* porcine muscle and fat samples were exposed to ultrasound at power levels that induce temperature elevation. In both tissue types, below the coagulation threshold, the USAE amplitude was found to vary linearly with temperature. However, at higher powers, the correlation with temperature was lost due mainly to the irreversible nature of the changes in the tissue properties. Theoretical simulations were used to interpret the USAE response change with temperature involving both reversible and irreversible changes and during both heating and cooling. These results indicate that USAE may have important promise as a potential method for localizing temperature elevation and, thus, thermal surgery monitoring, as well as detection of irreversible changes in tissues. (E-mail: elisak@bwh.harvard.edu) © 2002 World Federation for Ultrasound in Medicine & Biology.

**Key Words:** Fat, Focused ultrasound, Muscle, Lesion, Noninvasive, Surgery, Temperature, Thermal coagulation, Thermal therapy, Thermometry.

### INTRODUCTION

Minimally invasive thermal therapies, such as interstitial RF, microwave, laser (Haines 1992; Farahani et al. 1995; Zimmer et al. 1995; Jolesz et al. 1988) or noninvasive focused ultrasound (Fry et al. 1955; Hynynen et al. 1989; ter Haar 1995), are based on tissue coagulation resulting from a localized temperature elevation. The temperature elevation in living tissues induced by any of these energy delivery methods depends on the local physical properties of the tissue that determine the amount of energy absorption and the local heat transfer induced by thermal conduction and blood perfusion (Billard et al. 1990; Hynynen et al. 1989). These properties can vary significantly between different tissues, and even between locations in the same tissue. Therefore, a given power of

any of the thermal surgery devices can yield variable volumes of treated tissue and, thus, inconsistent clinical results. To overcome this uncertainty, the temperature elevation has to be locally monitored and controlled during treatment. Several imaging methods have shown promise in the monitoring and control of thermal therapies, with diagnostic ultrasound and magnetic resonance imaging (MRI) demonstrating the most potential (Hynynen et al. 1993; Chung et al. 1999). Several authors have previously discussed the temperature dependence of tissue stiffness (Van Kleef et al. 1978; Wu et al. 2001) and tissue absorption (Bamber and Hill 1979; Bush et al. 1993; Damianou et al. 1995b).

Ultrasound stimulated vibroacoustography, or ultrasound-stimulated acoustic emission (USAE) (Fatemi and Greenleaf 1998), is a recently developed imaging technique that applies a localized harmonic excitation inside a target through the application of two focused beams that oscillate at slightly different frequencies. These two beams overlap only at the focus of the transducer and

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generate a radiation force that causes the target to locally vibrate at the beat frequency. The response recorded at the hydrophone depends on both the local acoustic and mechanical properties of the target. Karjalainen et al. (1999) showed that the amplitude of the USAE signal is temperature-dependent. Konofagou et al. (2001) theoretically demonstrated that the tissue properties of stiffness and absorption influence the magnitude of the USAE signal in such a manner that it could be used to detect tissue coagulation. Therefore, in this study, we explored the dependence of the USAE signal on temperature and its potential use for temperature and thermal therapy monitoring. The proposed method may offer the most cost- and time-efficient way of monitoring thermal therapies. Furthermore, the system is simple compared to currently used imaging modalities. It consists of two focused ultrasound beams and a relatively simple detection system. These beams could be the same therapy beams used in focused ultrasound surgery (FUS).

In this paper, we demonstrate the dependence of the USAE amplitude on temperature, whether and how it can be used for temperature detection and monitoring, and show how it can indicate the onset of coagulation. The method was tested on *ex vivo* porcine muscle and fat tissues. In the appendix, finite-element simulations are used to interpret the experimental results.

## METHODS

### Sample preparations

Fresh porcine thigh muscle and subcutaneous fat tissue samples were excised from euthanized animals (7 pigs) and immediately immersed in a 0.9% saline. They were then kept refrigerated until the measurements were made; usually for 2 h. The approximate dimensions of the muscle and fat samples were  $5 \times 10 \times 10 \text{ cm}^3$  and  $10 \times 10 \times 8 \text{ cm}^3$  ( $1 \times w \times h$ ), respectively. The total number of measurement locations was 70. All the reported measurements were completed less than 10 h postmortem. The animal experiments complied with legal requirements and institutional guidelines.

### Experimental system

Two ultrasound beams with slightly different frequencies were generated by two transducer elements. A single circular PZT-4 transducer with a diameter of 100 mm and focal distance of 80 mm was divided into these two elements by cutting the bowl in half so that the areas of both elements were the same. The electrical impedance of each of the transducer elements was matched to  $50 \Omega$  near the resonance frequency of the crystal of 1.62 MHz using simple inductor-capacitor circuitry. The driving radiofrequency (RF) signals were obtained from two function generators (DS 345; Stanford Research Sys-

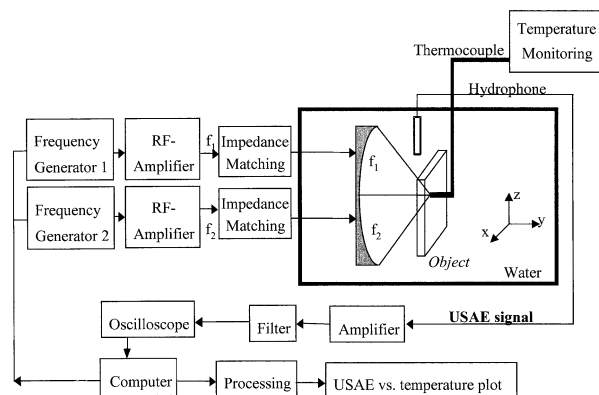


Fig. 1. A schematic picture of the measurement system used in this study.

tems, Sunnyvale, CA) controlled by a personal computer (PC) *via* an IEEE-488 communication line. One RF amplifier was used (models 3100L and A150; Electronic Navigation Industry, Rochester, NY) to drive each piezoelectric crystal element. The acoustic power was calibrated by using a radiation force technique on an absorbing target (Hill 1970), and these measurements were used to obtain equal acoustic power from both transducers. The transducer was mounted on a 3-D positioning system (Unislides; Velmex Inc., Bloomfield, NY) and immersed in a tank of degassed water to ensure good acoustical coupling (Fig. 1). A 3-D controller (NF90; Velmex Inc.) for the positioning system was connected to the PC *via* a RS-232 line.

The tissue samples were firmly attached in a holder that was positioned perpendicular to and in the focal zone of the beam in a water tank (Fig. 1). The holder consisted of two U-shaped Plexiglas sheets, between which the sample was inserted. The low-frequency USAE signal was detected by a radially omnidirectional hydrophone (AQ-18; Benthos Inc., North Falmouth, MA) that was positioned in the water tank between the transducer and the sample. The signal received from the hydrophone was bandpass filtered in the range from 500 Hz to 25 kHz using a differential amplifier (model 1820; Preamble Instruments, Beaverton, OR) and the resulting signal was registered with a digital oscilloscope (model 2431 L; Tektronix, Wilsonville, OR). The data were then transferred *via* an IEEE-488 communication BUS to a PC that also controlled the signal generators and the positioning system.

### Heating and cooling measurements

A bare junction twisted pair copper-constantan thermocouple (wire diameter:  $50 \mu\text{m}$ ) was placed inside the tissue for the temperature measurements. The two-ele-

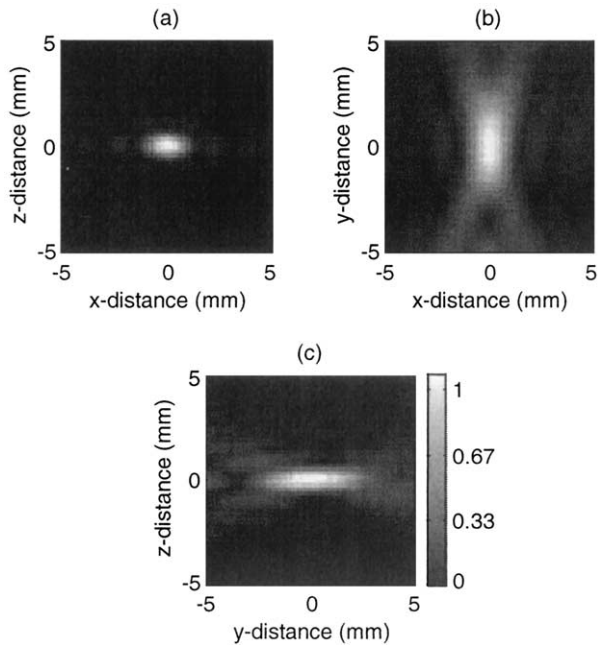


Fig. 2. Images of the (a) x-z, (b) x-y and (c) y-z normalized pressure fields of the two-element transducer. The  $-3$  dB beamwidth was estimated from (a).

ment transducer was positioned so that the thermocouple was located at the focal intersection point of the two beams (Fig. 1). The  $-3$  dB beamwidth at the focus was equal to 1.3 mm (Fig. 2). One of the transducer elements was driven at 1.62 MHz while the other was chirped from 1.62 to 1.64 MHz (99 steps, 50 ms duration). The USAE response was calculated through averaging of spectral amplitudes in a band from 18 kHz to 20 kHz. The chirp function was selected to obtain a less frequency-dependent USAE amplitude. The sonications were successively applied on the same tissue location using both elements at the same acoustical powers (per element) of 6.6 W (low power, fat; low power, muscle), 10.6 W (high power, fat) and 17.2 W (high power, muscle). Continuous wave (CW) sonications using one of the two elements lasted 100 s and 380 s at low power and 60 s and 160 s at high power in the fat and muscle, respectively. Cooling measurements using both elements at pulsed-wave (PW) were taken over 80 s and 200 s at low power and 120 s and 320 s at high power in the fat and muscle, respectively. Control measurements (*i.e.*, at constant room temperature) were taken over 20 s before every sonication. Temperature (*i.e.*, thermocouple) and USAE measurements were made every 2 s both during heating and cooling. During the cooling period, the ultrasound beams were turned on for 15 ms at a time. These USAE measurements were performed by pulsing the two beams at one of the aforementioned powers for

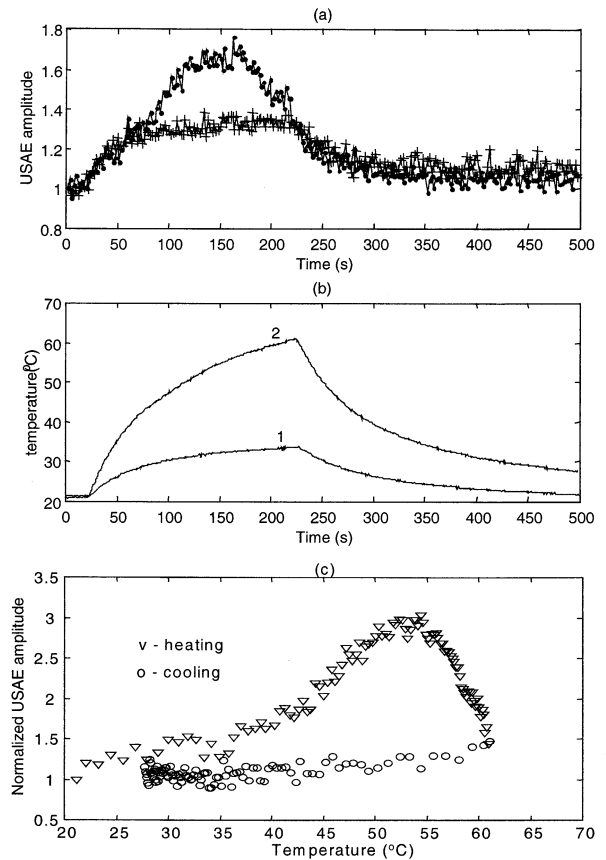


Fig. 3. (a) USAE amplitude variation at 6.6 W (+) and 17.2 W (•••); (b) Temperature variation at 6.6 W (1) and 17.2 W (2) in a porcine muscle sample; and (c) USAE amplitude variation at high power (17.2 W) with temperature (to be compared to the theoretical result of Fig. 7).

50 ms. Three measurements were taken from each sample; one at the thermocouple location inside the tissue and two 20-mm away from the thermocouple on either side. The temperature elevation in the last two locations was assumed to be the same as in the measurement at the thermocouple. Whenever cavitation occurred, as indicated by wideband noise in the hydrophone (Hynynen 1991), the corresponding data were ignored. Finally, the USAE amplitude shown in the Results section is normalized to its initial control value.

## RESULTS

Figures 3 and 4 summarize the results obtained from the muscle and fat samples, respectively. In both tissue cases, at low power (*i.e.*, below the coagulation threshold), the USAE response followed the temperature change (*i.e.*, during heating it consistently increased with temperature and during cooling it consistently decreased). In the muscle example (Fig. 3), at low power,

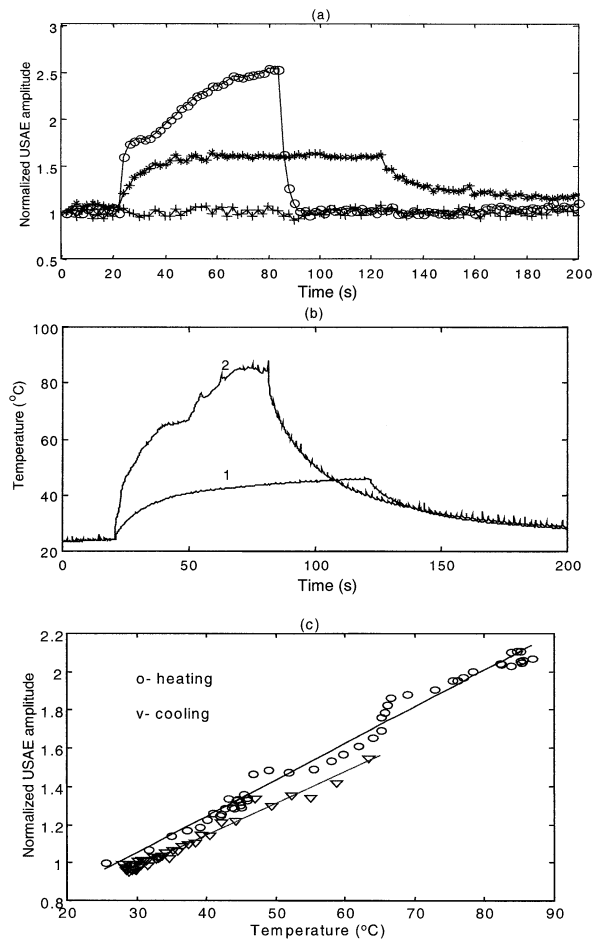


Fig. 4. (a) USAE amplitude variation at 6.6 W (\*) and 10.6 W (○); (b) Temperature variation at 6.6 W (1) and 10.6 W (2) in a fat sample. The results with water are also shown at 6.6 W (+) (no temperature measurements were obtained in the water).

because the temperature did not exceed 45°C (Damianou et al. 1995a), the changes made in the tissue were assumed reversible. At that power, the USAE amplitude variation shows an exponential rise and decrease during heating and cooling, respectively and, thus, follows that of the temperature. At high power, however, the correlation between USAE amplitude and temperature is lost beyond the temperature of 55°C, when muscle tissue typically coagulates (Wu et al. 2001). The USAE amplitude is shown to decrease with temperature while heating continues.

In the fat sample (Fig. 4), however, at both powers the correlation still holds, being highest at the lowest power, when the temperature stays below the coagulation threshold. Again, the USAE amplitude can detect small temperature changes below the irreversibility level at low power. The water measurements, which were taken after the sample was removed, are also shown here to

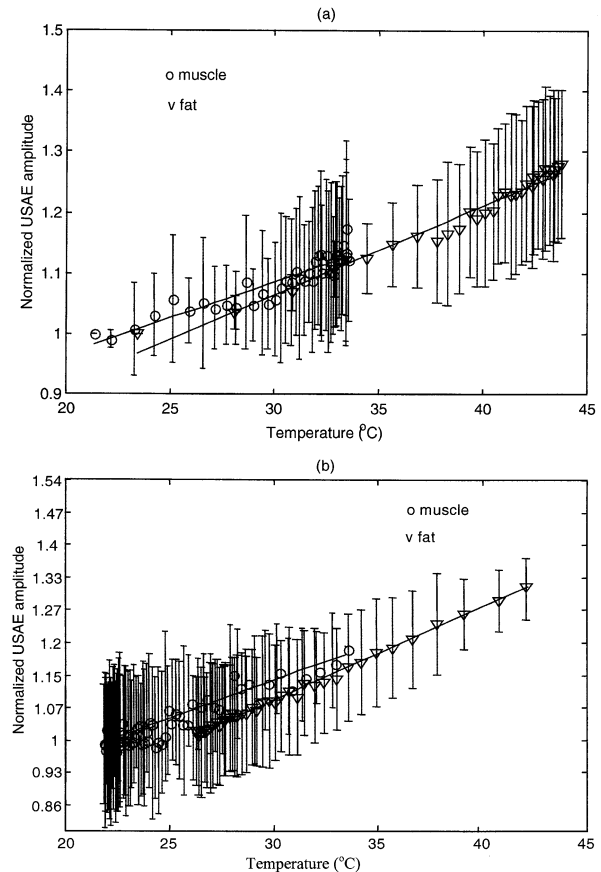


Fig. 5. Low power (6.6 W) normalized USAE amplitude in fat and muscle tissues with time during (a) heating and (b) cooling in nine points in seven different porcine samples.

demonstrate that the response from the tissue (and not the embedding water) resulted in the USAE amplitude change.

Figures 5 and 6 demonstrate the close dependence of the USAE variation on temperature during both heating and cooling at low and high powers, respectively. Because the overall trend of the USAE variation needs to be correlated with temperature, error bars show the standard deviation over nine distinct locations in the seven tissue samples, excluding thermocouple location and cavitation effects because the presence of the thermocouple in the focus was repeatedly shown to affect the measurements. At low power, during heating (Fig. 5a) and cooling (Fig. 5b), the muscle and fat tissues both show a linear variation with temperature and similar rates of variation. In the muscle, the normalized signal increases by 0.0118/°C ( $r^2 = 0.85$ ) during heating and decreases by 0.0086/°C ( $r^2 = 0.7$ ) during cooling. In the fat, the signal increases by 0.0147/°C ( $r^2 = 0.97$ ) during heating and decreases by 0.0146/°C ( $r^2 = 0.99$ ) during cooling. At high power during heating (Fig. 6a), the

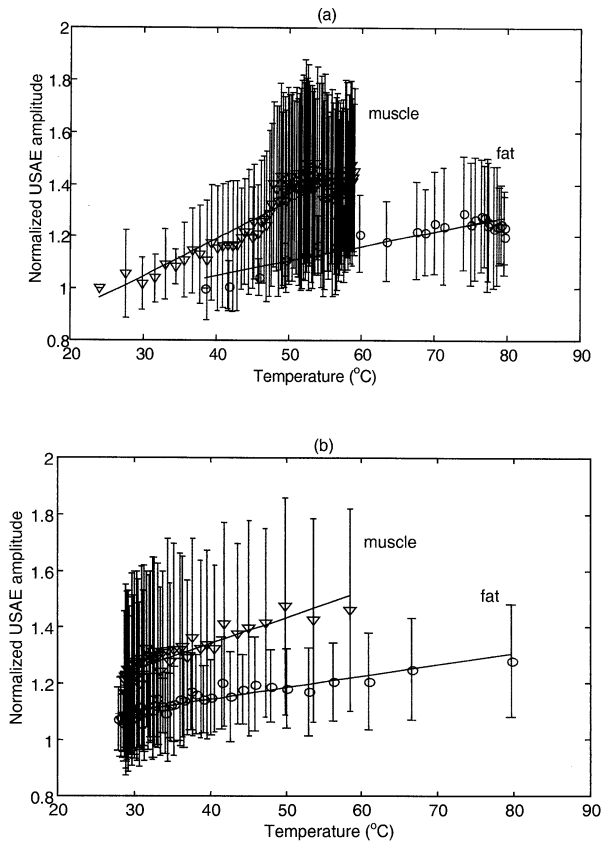


Fig. 6. High-power normalized USAE amplitude in the fat (10.6 W) and muscle (17.2 W) tissues with time during (a) heating and (b) cooling in nine points in seven different porcine samples.

USAE amplitudes also follow a linear variation with temperature, up to around 50°C and 75°C for the muscle and the fat, respectively, when the rates of variation in both tissues change. Nevertheless, a linear fit is also provided here for comparison to the low-power case. In the muscle, the signal increases by 0.0143/°C ( $r^2 = 0.83$ ) during heating (Fig. 6a) and decreases by 0.0092/°C ( $r^2 = 0.8$ ) during cooling (Fig. 6b). In the fat, the signal increases by 0.0056/°C ( $r^2 = 0.83$ ) during heating (Fig. 6a) and decreases by 0.0041/°C ( $r^2 = 0.835$ ) during cooling (Fig. 6b). The linear fit parameters also indicate lower correlation of the USAE amplitude with temperature in the fat at high power and the slightly higher correlation with temperature in the fat than in the muscle samples at low power. This could be attributed to the higher uniformity of the fat tissues and the resulting lower intravariability. Finally, the USAE variation with temperature deviates less from linear dependence during cooling than during heating, due possibly to the lack of interference of the CW beam in the former case.

Table 1. Stiffness (Wu *et al.* 2001) and absorption (Damianou *et al.* 1995b) values used in the simulation at different temperatures as indicated during heating (up to 73°C) and cooling (from 72.5°C to 32°C)

Temperature (°C)	Shear modulus (kPa)	Absorption (Np/m/MHz)
27	78	5.00
29	68	5.00
31	65	5.00
33	60	5.00
38	55	5.00
42	45	5.00
46	40	5.00
51	50	5.00
56	40	5.44
59	28	5.89
62.5	35	6.33
66	40	6.78
69	60	7.22
71	85	7.67
72	120	8.11
72.5	135	8.56
73	140	9.00
72.8	160	9.00
67	180	9.00
59	190	9.00
49	215	9.00
42	240	9.00
39	235	9.00
36	240	9.00
32	255	9.00

## DISCUSSION

Temperature monitoring during thermal surgery still remains one of the most crucial components of the treatment. In this paper, we present a method that uses US-stimulated acoustic emission to monitor temperature change during both heating and cooling. Experimental results showed that the USAE signal is temperature-dependent in both fresh *ex vivo* muscle and fat samples. In the appendix, finite-element simulations were used to predict the USAE response change with temperature. Previously reported results on the behavior of stiffness and absorption during heating and cooling were incorporated into the finite-element model to calculate the mechanical response from the center of the target with temperature. Simulations predicted a nonsymmetrical variation of the response at high powers (causing coagulation, beyond the irreversibility threshold), with it rising and decreasing during heating and cooling, respectively, but at different rates of change during the two distinct effects (Fig. 7). This result compares well with the experimental results in Fig. 3c.

The aforementioned experimental results, as well as their close comparison with preliminary simulations, offer some important conclusions. First, both small and high temperature changes can be detected. Second, stiff-

ness of the tissue influences the USAE response. This was concluded because we were able to measure USAE response change in the range where the absorption coefficient of the tissue did not vary (below 55°C, Table 1). This finding is tremendously important in the area of thermal surgery monitoring, where the stiffness of the tissue during coagulation can change up to 1 order of magnitude. Furthermore, this result has a more general significance, establishing once again that USAE is, indeed, sensitive to stiffness changes. Third, absorption also affects the tissue response. Its variation during coagulation of the tissue generates a different rate of change in the USAE variation with temperature and underlines the irreversible nature of the changes caused during sonication.

USAE measurements during cooling correlated better with temperature than during heating and typically followed an exponential decrease. During heating, because an additional radiation force was applied due to the CW sonication, the USAE variation was slightly more complicated. Also, at higher power levels, the onset of coagulation and the irreversibility of acoustical and mechanical changes resulted in the higher spread in the measurements obtained from various tissue samples. Furthermore, compared to the lower power results (Fig. 5), the spread of the measurements is higher at high powers (Fig. 6), mainly due to the irreversible changes that may differ from sample to sample. The fat shows lower standard deviation, possibly because it is more homogeneous than the muscle and, thus, less sample-dependent. At low power cooling, the USAE measurements have the lowest correlation with temperature in the muscle. This could be attributed to the fact that the temperature stays at low levels, challenging thus the sensitivity of the USAE system. Finally, the rates of variation of USAE amplitudes with temperature in the fat and muscle tissues are similar at low powers, but fairly distinct beyond the threshold of coagulation. This is probably due the different coagulation thresholds and tissue absorptions involved.

The experimental findings also indicated that the USAE signal was sensitive enough to allow localization of the hot spot at temperature levels that do not cause tissue damage. As a result, it was demonstrated that it may even be possible to predict the required power level for thermal coagulation of the tissue. In the muscle, the close correlation with temperature was lost following tissue coagulation. The loss of correlation between the USAE amplitude and temperature may, thus, be indicative of the onset of coagulation in the tissue. Wu et al. (2001) have, in fact, shown that the bovine muscle stiffness starts increasing beyond 55°C and this may help explain the amplitude decrease beyond that threshold. In other examples (not shown here), the response was

shown to change the rate of increase beyond the threshold of coagulation, possibly due to the increase in absorption beyond 45°C (Damianou et al. 1995b). Therefore, the loss of correlation of the USAE response with temperature may constitute a detection tool for the onset of coagulation. In the case of the fat, no physical explanations can be given at this point because, to our knowledge, the stiffness variation of fat tissue with temperature is not known. This change in the USAE signal may allow the mapping of the coagulated tissue volume after thermal exposure; thus, providing another method for monitoring the effectiveness of the treatment. Finally, its dependence on stiffness renders a more general role for USAE into the detection of stiffer materials, such as tumors.

These initial results and their theoretical verification demonstrate the feasibility of thermal therapy monitoring and justify more research exploring this technology. However, the current temperature resolution is not adequate for accurate temperature control. Future investigations will include corroborations with mechanical measurements of the same tissues as well as *in vivo* thermal therapy and surgery applications. If the results hold *in vivo*, USAE may be proven useful in monitoring temperature variations, not just with focused ultrasound surgery or hyperthermia, but also with other thermal treatment methods.

## CONCLUSION

In this study, it was shown that the method of ultrasound-stimulated acoustic emission can be utilized in conjunction with focused ultrasound to yield a reliable method for temperature detection and monitoring. Experimental findings on *ex vivo* porcine muscle and fat samples were qualitatively corroborated using finite-element simulations. The results demonstrated that the method depends on both the stiffness and absorption of tissues, that it could detect small temperature changes, highlight the onset of coagulation as well as differentiate between reversible and irreversible property changes caused during sonication. Should these results also be demonstrated in future *in vivo* applications, this method could be shown very promising in monitoring hyperthermia and ultrasound surgery as well as other thermal therapy techniques.

*Acknowledgements*—This research was funded by NIH grant CA82275.

## APPENDIX

### *Theory and simulations*

*Theory.* A radiation force (Torr 1984) is generated by changes in the energy density of an acoustic field.

Hence, a radiation force can be generated, for example, by sound reflection or absorption. The USAE method produces this force with two intersecting focused ultrasound beams of different frequencies (Fig. 1). The field energy density is sinusoidally modulated only at the intersection area and, hence, a highly localized oscillatory radiation force can be generated. The harmonic radiation force results in the harmonic displacement of the tissue, which is found through the solution of the following equilibrium equation in a linear time-invariant system (Rao 1995):

$$[m]\{\ddot{x}\} + [d]\{\dot{x}\} + [k]\{x\} = F, \quad (\text{A1})$$

where  $m$ ,  $d$  and  $k$  are the mass, damping and stiffness matrices of the system and  $x$  is the displacement, given by the steady-state solution of eqn. (A2)

$$x = X_o \cos(2\pi f_0 t), \quad (\text{A2})$$

where  $f_0 = f_2 - f_1$  and  $X_o$  is the amplitude of vibration equal to:

$$X_o = \frac{1}{k - m(2\pi f_0)^2} F_o. \quad (\text{A3})$$

In a simplified model (Konofagou *et al.* 2001), the resulting harmonic displacement of the tissue is given by:

$$x = \frac{4\alpha A}{cS(k - m(2\pi f_0)^2)} \cos(2\pi f_0 t), \quad (\text{A4})$$

where  $f_0 = f_2 - f_1$  is the excitation frequency,  $A$  is the amplitude of the beams,  $\alpha$  is the absorption coefficient of the tissue sonicated,  $c$  is the speed of sound in the tissue,  $S$  is the area of intersection of the two beams and  $k$  is the local stiffness. Therefore, the amplitude of the acoustic field is proportional to the acoustic ( $a$ ) and mechanical ( $k$ ) properties of the object. It has been shown that the absorption coefficient stays constant with temperature up to a certain temperature, when it starts increasing linearly with temperature (Damianou *et al.* 1995b; Table 1). The stiffness follows a more complex variation with temperature (Wu *et al.* 2001) (Table 1). Although measurements of stiffness changes of fat tissue with temperature has not been reported to our knowledge, Wu *et al.* (2001) have estimated the shear modulus of muscle tissue at different temperatures using MR elastography. Their results are given in Table 1. By using the absorption and stiffness measurements as reported in literature, these finite-element simulations allowed us to test the role of absorption and stiffness in the temperature-dependent changes observed in *ex vivo* porcine muscle and fat. The speed of

sound-dependence was not taken into account in these simulations because it has been shown that the effect on the focus, also known as lens effect, is minimal (Hallaj *et al.* 2001; Simon *et al.* 1998).

*Simulation methods and results.* Soft tissue was modeled on ALGOR (Algor, Inc., Pittsburgh, PA) by a triangular axisymmetric finite-element grid of size  $20 \times 40 \text{ mm}^2$  containing a 4-mm diameter ellipsoidal lesion in its center, typical size of lesions measured during the experiments reported in the main text. The entire grid (or, background), except for the lesion area, had a fixed shear modulus equal to 78 kPa, which was within the typical modulus range for normal soft tissues (Krouskop *et al.* 1998). The total number of nodes and elements was 714 and 1322, respectively, with 0.54 mm average node spacing. The Poisson's ratio and the density of all elements were equal to 0.499 and  $1000 \text{ kg/m}^3$ , respectively. The model was axisymmetric and the beam was assumed to perturb the tissue along its symmetry axis and in the middle of the lesion. All boundaries of the model were physically fixed and the frequency of excitation was set to 20 kHz, on the same order as that used for the experiments. The resulting harmonic displacement was estimated over the course of 10 ms with a 250-kHz sampling frequency. The amplitude of the displacement was estimated using the power spectrum (Konofagou *et al.* 2001).

Before temperature rise, the elements of the lesion had the exact same mechanical parameters as the background (or, normal tissue). To simulate the tissue during temperature increase, the elements of the lesion had distinct stiffness and absorption coefficient from the surrounding elements. Those parameters were modified according to the reported literature in the temperature range of 27 to 73°C for muscle, respectively (Table 1). The new stiffness value at each temperature was taken from the Wu *et al.* (2001) estimated shear modulus curve. The finite-element solution was then calculated for each stiffness value. The amplitude of the solution was then weighed by the absorption coefficient corresponding to the same temperature (Table 1). During heating, the absorption coefficient was varied with temperature according to prior experimental findings for muscle tissue at 4 MHz (Damianou *et al.* 1995b). During cooling (beyond 73°C), the absorption coefficient was assumed to sustain a constant value equal to the one achieved at the end of heating (Damianou *et al.* 1995b).

Figure 7 shows the normalized displacement amplitude with temperature within the temperature reported in the literature beyond coagulation. After coagulation, the linear relationship of amplitude vs. temperature is lost and the amplitude decreases with temperature. This result is comparable to what was found in the muscle at

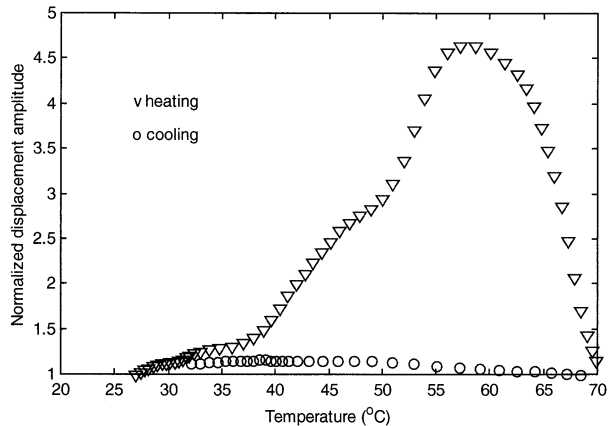


Fig. 7. Variation of the displacement amplitude with temperature in high-power muscle simulations.

high power (Fig. 3c). In the experiments, the maximum signal was approximately 3 times higher than the control value. The simulations showed an increase by 4.5 times. Finally, in both simulations and experiments, the response at the end of cooling is higher than the original due to the irreversible nature of the stiffness and absorption changes. A similar behavior could also be corroborated in the example of *ex vivo* rabbit liver results, as reported by Karjalainen et al. (1999). These results indicate that the simulation model is taking into account the major factors influencing the USAE signal. However, we note here that, because the stiffness estimations used in the simulations were generated using a different system and different tissues (bovine instead of porcine muscle), the comparisons between simulations and experiments are only used for a qualitative analysis of the overall behavior of the USAE response with temperature.

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