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Characterization of lesion formation and bubble activities during high-intensity focused ultrasound ablation using temperature-derived parameters

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HIGHLIGHTS

- IR imaging is applied to measure temperature changes during HIFU ablation.
- Temperature-derived parameters corresponding to tissue changes are identified.
- An increase in temporal rate of temperature indicates lesion formation.
- Spatially asymmetric temperature changes indicate bubble and/or cavity formation.
- The critical equivalent minutes at 43 °C for myocardium is determined to be 170 min.

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ABSTRACT

Successful high-intensity focused ultrasound (HIFU) thermal tissue ablation relies on accurate information of the tissue temperature and tissue status. Often temperature measurements are used to predict and monitor the ablation process. In this study, we conducted HIFU ablation experiments with *ex vivo* porcine myocardium tissue specimens to identify changes in temperature associated with tissue coagulation and bubble/cavity formation. Using infrared (IR) thermography and synchronized bright-field imaging with HIFU applied near the tissue surface, parameters derived from the spatiotemporal evolution of temperature were correlated with HIFU-induced lesion formation and overheating, of which the latter typically results in cavity generation and/or tissue dehydration. Emissivity of porcine myocardium was first measured to be 0.857 ± 0.006 ($n = 3$). HIFU outcomes were classified into non-ablative, normal lesion, and overheated lesion. A marked increase in the rate of temperature change during HIFU application was observed with lesion formation. A criterion using the maximum normalized second time derivative of temperature change provided 99.1% accuracy for lesion identification with a 0.05 s^{-1} threshold. Asymmetric temperature distribution on the tissue surface was observed to correlate with overheating and/or bubble generation. A criterion using the maximum displacement of the spatial location of the peak temperature provided 90.9% accuracy to identify overheated lesion with a 0.16 mm threshold. Spatiotemporal evolution of temperature obtained using IR imaging allowed determination of the critical cumulative equivalent minutes at 43 °C (CEM_{43}) for lesion formation to be 170 min. Similar temperature characteristics indicative of lesion formation and overheating were identified for subsurface HIFU ablation. These results suggest that parameters derived from temperature changes during HIFU application are associated with irreversible changes in tissue and may provide useful information for monitoring HIFU treatment.

1. Introduction

High-intensity focused ultrasound (HIFU) is a promising modality for non-invasive, targeted thermal tissue ablation [1,2]. HIFU induces tissue coagulation (thermal lesion) by localized heating from thermoviscous absorption of ultrasound energy; hence accurate information of the tissue status (e.g., native, coagulated, or with cavities) during HIFU application in the targeted region is important for providing feedback to ensure the desired HIFU outcome.

Lesion formation via tissue coagulation depends on the thermal dose, which is determined by the cumulative effect of thermal

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energy deposited in the tissue, based on the activation energy required for protein denaturation in tissue [3,4]. The cumulative equivalent minutes at 43 °C (CEM_{43}) metric, which is the equivalent time duration (in minutes) calculated from temperature time history to cause tissue damage if the temperature were kept at 43 °C [5–7], has been used widely for assessment of thermal dose needed for tissue coagulation. A critical CEM_{43} of 240 min has been used extensively to predict tissue coagulation in kidney, liver, and muscle [8,9], although CEM_{43} varies across species as well as tissue types [7]. The true threshold is often difficult to obtain due to the difficulty in determining the temporal temperature profile during lesion formation.

Thus in addition to methods that can directly determine the tissue status, methods capable of accurately measuring tissue temperature during HIFU application can be useful for monitoring and guiding HIFU ablation. Typically, the tissue temperature evolves as a function of time and spatial location as described by the bioheat equation [10–12]. The temperature measurements are used to estimate tissue coagulation, if a deterministic relationship has been established for such correlation.

Thermocouples can be used to measure temperature at discrete locations where they are inserted [13,14], but they disrupt HIFU field and often are not feasible for *in vivo* use. Also viscous heating and thermal conduction by thermocouples themselves during HIFU application may introduce error in measurements [15–17]. Ultrasound imaging and magnetic resonance imaging (MRI) have been used to provide non-invasive temperature measurements for HIFU applications [18–21], although this approach is subject to artifacts [22,23], and is limited by insufficient acquisition speed [17] and the high cost of MRI.

During HIFU application, lesion formation results in changes of the thermal, mechanical, and acoustical properties of the tissue. These changes, along with other events induced by HIFU heating, can alter the course of temperature evolution. In particular, degassing, boiling, vaporization, and cavitation in tissue [24,25] often occur due to excessive heating, rapid temperature increase, and high level of acoustic pressures. In some cases, the combined effect of high acoustic pressure and rapid heating may generate unwanted macroscopic cavities or tissue fragmentation. These events, which result in destruction of local tissue integrity and changes of material properties, not only cause inefficient ablation of distal tissue segments [26] and altered lesion location, shape, and size from the original treatment plan, but also render the prediction of tissue status from temperature measurement difficult.

Infrared (IR) thermography, although limited to surface measurements, can obtain accurate measurements of temperature changes as a function of space and time directly without contact. The advantages also include easy implementation, high temporal (up to 100 Hz) and spatial resolution (down to 100 μm). IR imaging is useful for diagnosis and treatment monitoring, as demonstrated by medical applications such as oncology (breast cancer, skin diseases), skin burns, vascular disorders, surgery, tissue viability, and mass screening [27–29]. Laparoscopic IR systems have also been developed and used in assessing tissue necrosis during radiofrequency ablation [27] and tested on porcine models to provide additional anatomic and physical details from the differences in temperature between adjacent structures and organs [29,30].

The goal of this study is to derive parameters from spatiotemporal changes of IR-measured temperature and determine whether they are correlated with relevant events during HIFU application (e.g., lesion formation, cavity formation), in order to provide useful markers for HIFU ablation monitoring.

We conducted experiments using *ex vivo* cardiac tissue, for the purpose of ultimately improving HIFU ablation of cardiac arrhythmia [31,32]. We used IR imaging to measure tissue surface temperature during HIFU ablation. We first conducted experiments with the HIFU focus placed close to and slightly below the tissue surface where lesion formation and other events can be observed on the surface. In this way, changes in temperature-derived parameters related to lesion formation, overheating and bubble formation during HIFU application could be identified to permit corroboration of tissue changes with temperature measurements by IR imaging. This registered observation also allows computation of the thermal dose and determination of the critical CEM_{43} for myocardium tissue. We also extended our experimental studies to subsurface HIFU ablation to identify the characteristic temperature behaviors in this context.

2. Materials and methods

2.1. Tissue specimens and emissivity measurement

Ex vivo porcine myocardium tissue specimens obtained from a local abattoir were used in this study. For calibration of IR imaging, a flat surface of the tissue specimen was imaged with the IR camera perpendicular to the surface. Emissivity for myocardium was measured using the black tape method [33] where the Scotch Super 33+ Vinyl Electrical Tape (3M Company, St. Paul, MN, USA) with a known emissivity of 0.95 was used. The emissivity of coagulated myocardium was also measured after coagulation in a microwave oven, where different levels of dehydration were generated by applying various durations of microwave exposure.

2.2. Experimental setup and IR imaging

We used an IR camera (Silver 5600, FLIR Systems, Boston, MA, USA) sensitive to the mid-IR wavelength range (3–5 μm), with a temperature measurement accuracy of ±1 °C and a resolution of 0.01 °C (Fig. 1). IR imaging was performed using two integration (exposure) times for measurements ranging from 15 °C to 120 °C, and conversion from IR radiance to temperature was performed using the manufacturer's calibration and non-uniformity corrections.

To generate HIFU exposures with adjustable amplitude and duration, the HIFU system used two function generators (33220A, Agilent, Santa Clara, CA, USA), a power amplifier (325LA, ENI, Rochester, NY, USA), and a focused transducer (3.98 MHz center frequency, $F = 1$, Blatek, Inc., State College, PA, USA). The HIFU transducer was calibrated using a hydrophone (HNR-0500, Onda, Sunnyvale, CA, USA) and its −6 dB focal width and focal length were measured as 0.9 mm and 4.6 mm, respectively. Experiments were performed with the transducer submerged in water facing up towards a tissue specimen with its top surface above the water level

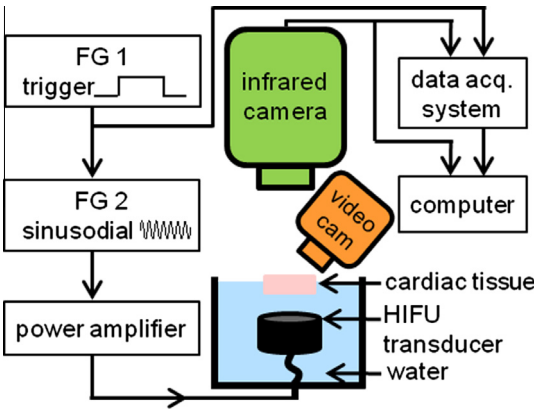

Fig. 1. Schematic diagram of the experimental setup.