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A study of latent heat effects in temperature profiles and lesion formation

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ABSTRACT

The concept of thermal dose is widely adopted in the simulation of thermal therapies to estimate the formation of ablation lesions. However, such approaches typically use empirical assumptions, and treat the formation of a lesion as an end result from heating and not as a factor that could influence the temperature profile. In this study, the forming of lesions during high-intensity focused ultrasound (HIFU) therapy is interpreted as a denaturation process involving an irreversible phase transformation, and is a critical factor influencing the evolution of the temperature profile. Based on this notion and HIFU experiments performed on the pork tenderloin and egg white-based gel phantom, an important but often neglected phenomenon during the formation of the HIFU ablation lesion – referred to as the thermal confinement – was revealed. The thermal confinement, resulted from latent heat effects, exhibits features such as a substantial time delay in reaching maximum temperature around the ultrasound focal spot after turning off HIFU, and a lower-than-expected peak temperature attained during the ablation. A theoretical model capable of predicting the thermal confinement phenomenon and the changes in the temperature profile associated with it was successfully constructed. In addition, a modified bioheat transfer equation with the effect of latent heat from denaturation was proposed. The simulated temperature profiles further revealed the extent of the influence of the thermal confinement is strongly dependent on the position relative to the ultrasound focal spot.

1. Introduction

The adoption of the bioheat transfer equation [1] and thermal dose concept [2,3] for predicting the effect of high-intensity focused ultrasound (HIFU) therapy has been well studied [4,5]. The procedure typically involves obtaining the temperature profile (i.e., temperature history and distribution) by solving the bioheat transfer equation first, followed by predicting the lesion size using the relationships of temperature and time. However, such an approach has two major shortcomings: a crude expansion of the original description of the thermal dose concept is commonly employed and the thermodynamic aspect of lesion formation and its effect on temperature profile are often ignored.

The original concept of thermal dose was that the effect of thermal therapy can be summarized by the relationship between the therapy acting time and the external temperature of the cells, i.e., therapy temperature [2,3]. In Dewey et al.'s experiments on heating Chinese hamster ovary (CHO) cells at different temperatures, information on the acting time t and acting temperature T of each heating case was collected and summarized. It was found that the ratio between the required treatment time for two different cases is equal to a certain constant R to the power of the temperature difference between the two cases. The relationship was defined by Dewey et al. (1977) as:

$$t_1 = t_2 R^{(T_1 - T_2)} \tag{1}$$

where subscripts 1 and 2 represent two different heating cases and constant R can be calculated by:

$$R = e^{-\Delta H/(2T(T+1))} \tag{2}$$

where ΔH is the enthalpy or inactivation energy of the CHO cells. In fact, R should not be considered strictly as a constant, but as a temperature-dependent variable. Nevertheless, R was claimed by Dewey et al. to be 0.50 for the CHO cells in the temperature range

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of 43–46 °C [2,3]. For the calculation of R as described by Eq. (2), a temperature increment step of 1 °C is adopted. Eqs. (1) and (2) indicate that if the cell external temperature is increased by 1 °C, the therapy acting time required is decreased R-fold.

Several empirical assumptions have since been incorporated into the thermal dose concept [2,3,5]. This results in the expansion of Eq. (1) to:

$$t_{ref} = \sum_{t=0}^{t=final} R^{(T_{ref}-\overline{T})}\Delta t \tag{3}$$

where T_{ref} is the reference internal tissue temperature, typically chosen as 43 °C, t_{ref} is the corresponding therapy time at T_{ref}, and $\overline{T}$ is the average internal tissue temperature during the time interval Δt. The constant R is still commonly used, but can be assumed to have different values for different temperature ranges [6]. The expansion of the thermal dose concept from cell to tissue and from cell external temperature to tissue internal temperature has been widely implemented in the existing studies on thermal therapy [4,5,7–11].

Nevertheless, the empirical parameters and assumptions needed for the expansion may not be suitable or accurate for all ranges of temperature. In this study, the forming of a lesion during thermal therapy is interpreted as a denaturation process involving an irreversible phase transformation. Consequently, part of the input energy is consumed without an increase in temperature during the formation of the HIFU ablation lesion, i.e., latent heat of phase transformation. In addition, the thermal properties of the tissue change when the lesion forms. The forming of lesions during thermal therapy is therefore not only a result of heating, but also has a significant effect on the history and distribution of the temperature profile. Such an influence was not considered in the original thermal dose concept and hence has been frequently overlooked in existing thermal dose models.

The motivation of the present study is to address this significant inadequacy in the original concept of thermal dose. To achieve this goal, the thermal phenomena of ablating pork tenderloins and egg white-based gel phantoms by HIFU are examined in detail. A theoretical model is developed to predict the thermal behaviors of HIFU therapy more accurately. Furthermore, numerical simulations based on the finite element method are performed to explain in detail the physical meaning of the proposed model, which intends to refine the thermal dose concept by incorporating features associated with the occurrence of denaturation, i.e., the formation of a lesion.

2. Materials and methods

2.1. High-intensity focused ultrasound system

The prototype HIFU system designed for the present study is shown in Fig. 1a. A 2 MHz sinusoidal waveform, in pulsed or continuous mode and produced by a function generator (33120A, Agilent, Palo Alto, CA, USA), was passed through a radio-frequency amplifier (150A250, Amplifier Research, Souderton, PA, USA), a power meter (4025, Bird Electronic Corp., Cleveland, OH, USA), and then a diplexer (RDX-2, Ritec, Warwick, RI, USA) before being fed into a 2 MHz focused piezoelectric transducer (SU-101, Sonic Concepts, Woodinville, WA, USA). The diameter of the transducer is 35 mm and the radius of curvature is 55 mm. The −3 dB contour of the focal zone measured by a needle hydrophone (SPEH-S-0500, ONDA, Sunnyvale, CA, USA) is 4.5 mm in length and 0.5 mm in width. The ultrasound produced by the transducer was aimed at a target sample (pork tenderloin or gel phantom) fixed in a $15 \times 15 \times 23$ cm degassed water tank. The focal spot of the ultrasound was positioned inside the target sample. The echo signal of the incident ultrasound, collected by the same piezoelectric transducer, was monitored by an oscilloscope (LT354ML, LeCroy, Chestnut Ridge, NY, USA) and processed by a fast analog-to-digital (A/D) converter (PCI-9820, Adlink Technology Inc., Taiwan). The spatial position of the transducer was controlled by a dual axis stepper motor (Jubilee Technology Corp., Taiwan) to an accuracy of 0.1 mm. Temperature near the HIFU focal spot was measured by a thermocouple data acquisition system (USB-9211A, National Instruments Taiwan, Taiwan, with J type thermocouples). All components of the prototype HIFU system were controlled and synchronized by the LabVIEW program (National Instruments Taiwan, Taiwan).

For the HIFU ablation experiment, a continuous wave with an average power density of ~2.1 kW cm^{-2} in the focal spot (typically produced from 10 to 12 MPa peak positive pressure and 60 W electrical power [12]) was delivered by the piezoelectric transducer. A thermocouple recorded the evolution of temperature with time near the ultrasound focal spot during the experiment. In order to prevent the temperature measurement from being influenced by the incident ultrasound, and also to establish a reasonable distance to allow the quantification of thermal conduction time, the thermocouple was positioned 4 mm away from the focal spot. The relative positions of the piezoelectric transducer, target sample, and thermocouple are shown in Fig. 1b. The prototype HIFU system was also utilized to ultrasonically image the target sample. For imaging operations, low-intensity sinusoidal waves in 5 kHz burst rate (3–5 cycles) were applied to the target sample and the echo signals were monitored by the same transducer and processed with a sampling rate of 120 MHz. Any change in the material properties of the target sample would give rise to changes in the peak position and intensity of the echo spectrum.

2.2. HIFU ablation of pork tenderloin

Fresh pork tenderloin was chosen as one of the sample materials for the HIFU ablation experiment due to its similarity to human soft tissue. The pork tenderloin was cut into a $4 \times 4 \times 6$ cm cuboid and placed in the degassed water tank using a plastic fixture frame. Due to the nonuniformity of the pork tissue, multiple echo peaks were generated, hindering the determination of the focal spot of the incident ultrasound. This complication was solved by determining the spatial position of the fixture frame first (from the large backscattered signal when the ultrasound focused on the plastic frame); by using the fixture frame as a positional reference, the ultrasound focal spot could be positioned at the center of the cuboid pork sample by moving the piezoelectric transducer. The pork sample was heated by the HIFU system for 60 s and the temperature at a position 4 mm away from the ultrasound focal spot was recorded during and after the ablation. The position, shape, and size of the ablation lesion produced were examined by sectioning the cuboid pork sample parallel to the ultrasound transmission direction and perpendicular to the surface normals. Fig. 1b shows schematically a sectional plane of the sample containing the ultrasound focal spot and the inserted thermocouple. The pork tenderloin sample was used to test the experimental setup. The data were not studied further because of the acoustical inhomogeneity of pork tissue, and because its opacity precluded observation of the formation of lesions.

2.3. Hypothesis of thermal confinement

The one-dimensional Fourier's law of heat conduction for describing heat flow from points 1 to 2 is given as:

$$\frac{dQ}{dt} = \frac{kA}{L}(T_1 - T_2) \tag{4}$$