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● *Original Contribution*

PREDICTING TISSUE SUSCEPTIBILITY TO MECHANICAL CAVITATION DAMAGE IN THERAPEUTIC ULTRASOUND

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Abstract—Histotripsy is a developing focused ultrasound procedure that uses cavitation bubbles to mechanically homogenize soft tissue. To better understand the mechanics of tissue damage, a numerical model of single-bubble dynamics was used to calculate stress, strain and strain rate fields produced by a cavitation bubble exposed to a tensile histotripsy pulse. The explosive bubble growth and its subsequent collapse were found to depend on the properties of the surrounding material and on the histotripsy pulse. Stresses far greater than gigapascals were observed close to the bubble wall, but attenuated by four to six orders of magnitude within 50 μm from the bubble wall, with at least two orders of magnitude attenuation occurring within the first 10 μm from the bubble. Elastic stresses were found to dominate close to the bubble wall, whereas viscous stresses tended to persist farther into the surroundings. A non-dimensional parameter combining tissue, waveform and bubble properties was identified that dictates the dominant stress (viscous vs. elastic) as a function of distance from the bubble nucleus. In a cycle of bubble growth and collapse, characteristic times at which mechanical damage is likely to occur and dominant mechanisms acting at each time were identified. (E-mail: lamancha@umich.edu) **© 2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Cavitation, Bubble dynamics, Simulation, Histotripsy, Tissue ablation.**

INTRODUCTION

High-intensity ultrasound pulses produce rapid pressure changes in tissue, thus giving rise to cavitation. As they grow and collapse, bubbles forming in low-pressure regions can cause damage to surrounding tissue. Acoustic cavitation dynamics in soft tissue has been a subject of growing interest since the development of non-invasive, focused ultrasound therapies. Treatments such as shock wave lithotripsy (SWL) and histotripsy directly rely on cavitation. In SWL, the erosive effect of collapsing bubbles contributes to fractionation of kidney stones (Bailey et al. 2003). Histotripsy is a non-invasive focused ultrasound procedure that uses cavitation generated by high-amplitude ultrasound pulses to mechanically destroy soft tissue (Parsons et al. 2006; Roberts et al. 2006; Xu et al. 2005). Experimental studies of histotripsy-induced cavitation in tissue phantoms and animal models have illustrated the influence of tissue mechanical properties such as elasticity on the cavitation threshold (Vlaisavljevich et al. 2014, 2015b) and bubble growth (Vlaisavljevich et al. 2015c). At present, however, the mechanisms responsible for tissue damage observed in histotripsy and other cavitation-inducing ultrasound treatments remain difficult to quantify. There is strong evidence that stiffer tissues are more resistant to cavitation damage. However, the mechanics of cell–bubble interactions and the influence of material properties, for example, shear modulus, viscosity and ultimate stress/strain, are less clear (Vlaisavljevich et al. 2013). An improved understanding of cavitation-induced tissue damage mechanisms will facilitate the development of effective means of planning and monitoring therapeutic ultrasound procedures, as well as improve the treatment's tolerability and efficacy (Miller et al. 2012). Understanding the influence of tissue properties on damage could enable optimization of treatment parameters for different tissues, which would be particularly important for the development of self-limiting and vessel-sparing clinical applications (Vlaisavljevich et al. 2013).

Multiple mechanisms for cavitation-induced damage during ultrasound procedures have been proposed,

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including shock waves and high temperatures at bubble collapse, as well as re-entrant jets produced during aspherical bubble collapse (Nyborg et al. 2002). Experimental observations (De et al. 2007; Vlaisavljevich et al. 2016a) indicate that local deformations in the vicinity of histotripsy bubbles can be considerable, occur rapidly and depend on the material properties. It is thus reasonable to hypothesize that cavitation-induced mechanical loading is a potential tissue damage mechanism in histotripsy. Correlations between high tensile strength and resistance to tissue damage also suggest that stress, in particular, contributes to tissue rupture in histotripsy (Vlaisavljevich et al. 2013). However, experimental measurements of local, highly transient, cavitation-induced stresses and strains are difficult to obtain because of limited spatiotemporal resolution and optical access (Zimberlin et al. 2007). To bypass these challenges, spherical bubble dynamics are numerically modeled in a soft material (Warnez and Johnsen 2015), thus quantifying localized stress and strain distributions in simulated tissues exposed to histotripsy pulses.

Deformations produced in viscoelastic media by single cavitation bubbles exposed to harmonic forcing have been computed previously (Church and Yang 2006). The current study is unique in providing independent consideration of different tissue mechanical properties and waveform characteristics on several proposed damage mechanisms (stresses, finite strains and strain rates) developed during cavitation under histotripsy forcing. Stress and strain fields are considered in different reference frames to facilitate experimental comparisons. The focus is to quantify proposed damage mechanisms to identify specific contributors to tissue damage and to provide a theoretical basis for the development and enhancement of damage metrics. Furthermore, recent experimental investigations of cells (neurons) exposed to large compressive strains at high rates revealed that a critical strain threshold must be met to produce cell death, but that the extent of cell death depends on strain rate (Bar-Kochba et al. 2016). The present work presents a means of identifying the relative influence of strain (dominated by tissue elasticity) versus strain rate (proportional to tissue viscosity) as a function of distance from the bubble wall, which could provide a more detailed prediction of lesion morphology in different tissue types.

The numerical methods in this study were previously used to complement experimental investigations of histotripsy-induced cavitation thresholds (Vlaisavljevich et al. 2014, 2015b, 2016b), bubble growth (Vlaisavljevich et al. 2015c) and cell–bubble interactions (Vlaisavljevich et al. 2016a). After description of the theoretical model and problem setup, methods for calculating field quantities are introduced. Next, the results of a simulation parameter study are provided to illustrate the influence of tissue (viscosity, shear modulus, nucleus size) and waveform (amplitude, frequency) properties on stress and strain developed in the tissue. Finally, a relationship is identified between the dominant contribution to viscous versus elastic stress and distance from the bubble nucleus.

THEORETICAL MODEL

Early theoretical models were developed to study bubbles driven hydrodynamically (Plesset 1949) and acoustically (Noltingk and Neppiras 1950) in liquids. More recently, non-Newtonian models have been used to investigate cavitation in viscoelastic materials representative of polymer gels (Shima and Tsujino 1982) and soft biological tissue (Brujan 2010). Several constitutive models have been adapted to the study of cavitation with the intention of mimicking the dynamics of bubbles in soft tissue, including the Maxwell (Allen and Roy 2000a), Kelvin–Voigt (Yang and Church 2005), Oldroyd (Allen and Roy 2000b) and Zener (Hua and Johnsen 2013) models. The present study simulates the dynamics of a single, spherical bubble in a compressible Kelvin–Voigt-based viscoelastic solid with non-linear elasticity (Gaudron et al. 2015), which accounts for the reference configuration of the tissue. Our model includes a hyperelastic term derived from finite-strain theory to adequately represent the large deformations encountered in the nanometer- to micron-scale bubble growth observed in histotripsy.

This study considers a spherical, homobaric bubble in an infinite, homogenous viscoelastic medium. To account for acoustic radiation losses, the bubble dynamics are described by the equation of Keller and Miksis (1980)

$$\left(1-\frac{\dot{R}}{c_\infty}\right)R\ddot{R}+\frac{3}{2}\left(1-\frac{\dot{R}}{3c_\infty}\right)\dot{R}^2=\frac{1}{\rho_\infty}\left(1+\frac{\dot{R}}{c_\infty}+\frac{R}{c_\infty}\frac{d}{dt}\right)\times\left[p_B-\left(p_\infty+p_f\left(t+\frac{R}{c_\infty}\right)\right)-\frac{2S}{R}+J\right], \quad (1)$$

where R is the bubble radius, c_∞ and ρ_∞ are the constant sound speed and density of the medium and S is the surface tension. The far-field pressure is the sum of the ambient pressure, p_∞, and time-varying ultrasound forcing, $p_f(t)$ (eqn [8]). The pressure of the non-condensable air inside the bubble is given by the polytropic relationship $p_B = p_0(R_0/R)^{3\kappa}$, where $p_0 = p_\infty + 2S/R_0$ is the pressure inside the bubble at equilibrium. Gas inside the bubble is assumed to behave isothermally with a polytropic coefficient $\kappa = 1$, which is expected to be an accurate representation of the heat transfer. For simplicity, the tissue–bubble boundary is assumed to be impervious to gas, and vapor inside the bubble is neglected. These assumptions could potentially underpredict the bubble

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