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● *Original Contribution*

INVESTIGATION INTO THE MECHANISMS OF TISSUE ATOMIZATION BY HIGH-INTENSITY FOCUSED ULTRASOUND

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Abstract—Ultrasonic atomization, or the emission of a fog of droplets, was recently proposed to explain tissue fractionation in boiling histotripsy. However, even though liquid atomization has been studied extensively, the mechanisms underlying tissue atomization remain unclear. In the work described here, high-speed photography and overpressure were used to evaluate the role of bubbles in tissue atomization. As static pressure increased, the degree of fractionation decreased, and the *ex vivo* tissue became thermally denatured. The effect of surface wetness on atomization was also evaluated *in vivo* and in tissue-mimicking gels, where surface wetness was found to enhance atomization by forming surface instabilities that augment cavitation. In addition, experimental results indicated that wetting collagenous tissues, such as the liver capsule, allowed atomization to breach such barriers. These results highlight the importance of bubbles and surface instabilities in atomization and could be used to enhance boiling histotripsy for transition to clinical use. (E-mail: jcsimon@uw.edu) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **High-intensity focused ultrasound, Atomization, Histotripsy, Boiling, Cavitation, Capillary wave, Instability.**

INTRODUCTION

Ultrasonic atomization is a process that occurs when an acoustic wave in liquid is directed toward an air interface (a pressure-release interface); the process is not simple when the incident wave is a plane wave, and it becomes even more complex when the incident wave is a narrow, focused beam. Although liquid atomization has been studied extensively since the discovery of atomization in 1927, there remains some doubt as to the exact mechanism (Rozenberg 1973; Simon et al. 2012). The most accepted hypothesis of liquid atomization, called the cavitation-wave hypothesis, states that atomization arises from a combination of cavitation bubble oscillations and capillary wave instabilities (Boguslavskii and Eknadiosyants 1969; Rozenberg 1973). Recently, it was reported that tissues could also be atomized and that such atomization occurs in the form of fractionation and expulsion of tissue from the surface (Simon et al. 2012). Yet questions remain as to the mechanism underlying tissue atomization, particularly the roles of bubbles and tissue properties in the fractionation and atomization of tissue. The goal of the work described in this article was to test experimentally the role of cavitation in the fragmentation and atomization of *ex vivo* tissue by suppressing bubble activity with overpressure. The effects of tissue properties were also investigated, in particular how the wetness of tissue and its surface affect the inception and success of atomization and surface erosion *in vivo* and in tissue-mimicking gels.

Tissue atomization was first explored to explain the mechanism of bulk tissue fractionation in a relatively new high-intensity focused ultrasound (HIFU) approach named boiling histotripsy (Simon et al. 2012). In boiling histotripsy, non-linear propagation effects result in the formation of high-amplitude shocks in the ultrasound pressure waveforms and shock-wave heating causes the formation of a millimeter-diameter boiling bubble at the transducer focus in milliseconds (Canney et al. 2010). Interaction of the incident ultrasound wave with the bubble results in the fractionation of tissue into its submicron components (Khokhlova et al. 2011; Wang et al. 2013).

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With thorough experimentation, it was found that a fountain could form and atomization could occur within a millimeter void that mimicked the HIFU-induced boiling bubble in tissue; that the end result of atomization was erosion of the flat tissue surface adjacent to the air; and that the atomized tissue expelled from the flat tissue surface was partially fractionated, though not to the extent observed in bulk boiling histotripsy (Simon et al. 2012). By better understanding the mechanism of tissue atomization, the safety and efficacy of tissue fractionation by boiling histotripsy can be enhanced in its further development and transition into a clinical therapy.

Several observations were made during these preliminary studies, leading to questions regarding the mechanism of tissue atomization. For example, in the initial studies it was observed that the time the *ex vivo* tissue spent submerged in phosphate-buffered saline (PBS) affected the rate of tissue atomization and erosion (Simon et al. 2012), leading to the idea that tissue wetness influences atomization. Submersion in PBS is known to cause tissue swelling because of the changes in cellular metabolism and differences in salt and sugar concentrations between the tissue and solution, which affect not only tissue wetness, but also the mechanical stiffness of the tissue (Boutilier 2001; Kaboyashi et al. 1991; Southard 2004). In addition, PBS could also influence atomization by forming a thin liquid layer on the tissue surface that could ease the formation of capillary waves or other surface instabilities. Another observation made during preliminary studies was that highly collagenous tissues such as the liver capsule are more difficult to atomize. This relates back to both boiling and cavitation-cloud histotripsy therapies, where it has been noted that highly elastic tissues, such as blood vessels, remained intact while the surrounding tissue was completely fractionated (Khokhlova et al. 2014; Vlaisavljevich et al. 2014). Investigation into the influence of tissue viscoelasticity and wetness on its atomization could help in determining the tissue types that can be successfully atomized, as well as enhancing our understanding of the fundamentals of the mechanisms of tissue atomization by ultrasound.

In liquids, the cavitation-wave hypothesis most accurately describes what is observed in atomization; however, in tissues there is much debate as to whether atomization can be similarly described. In this article, the hypothesis that bubbles are necessary for tissue atomization was tested. The effect of bubbles was controlled by applying excess static pressure to the tissue samples studied. Overpressure has been used in other ultrasonic applications such as HIFU thermal ablation and shock wave lithotripsy to assess the role of bubbles (Bailey et al. 2001; Bronskaya et al. 1968; Hill 1971; Khokhlova et al. 2006; Sapozhnikov et al. 2002). In this work, the role of cavitation in tissue atomization was established using a custom-designed overpressure chamber and a high-speed camera. In addition, the effect of tissue wetness on atomization was evaluated, considering the relative effects of bulk and surface wetness on the erosion volume in *ex vivo* tissues and tissue-mimicking gels. High-speed photography was also used to analyze atomization *in vivo*, and techniques to breach the collagenous porcine liver capsule were explored. Finally, the hypothesis of tissue fragment recirculation was investigated to explain the histologic differences between bulk boiling histotripsy and atomization. As atomization has been found to explain the mechanism of tissue fractionation in boiling histotripsy, the ultrasound frequency, pulse length and pulse repetition frequency were chosen based on those used in most of the previously reported boiling histotripsy studies (Khokhlova et al. 2011, 2014; Wang et al. 2013). Although the figures and supplementary videos included in this article illustrate single instances of atomization, they represent what was observed upon repeated experimentation.

METHODS

Effect of overpressure on atomization

The custom-built overpressure chamber with a 2.127-MHz aluminum-lensed HIFU transducer is illustrated in Figure 1. The transducer consisted of a flat, 40-mm-diameter, piezoceramic source and an aluminum lens with a center thickness of 10.8 mm and a focal length of 40 mm. The static pressure in the chamber was controlled using a compressed air cylinder with a regulator (ProStar 4092, Praxair, Seattle, WA, USA). To create a pressure-release interface at the focal plane with adequate acoustic coupling to the transducer, the lower half of the chamber was filled with water and the tissue sample was placed on a mesh platform with a center cutout and partially submerged in water. In turn, the mesh platform was placed on a hollow acrylic cylinder that fit around the transducer lens. The setup was designed for the distal pressure-release surface of a 1.5-cm-thick piece of tissue to be located in the transducer focal plane; however, with the expectation that the tissue would compress slightly during overpressure, a system was designed to raise and lower the mesh platform. An O-ring was placed in the groove between the aluminum lens of the transducer and the wall of the chamber, underneath the acrylic cylinder. The pipe for the hydraulically controlled water line was placed beneath the O-ring, to allow the hydraulic pressure to raise and lower the tissue, even under increased static pressure conditions. This was essential as once the chamber was sealed, the tissue could not be otherwise manipulated.

Before experimentation, the focal acoustic pressure waveforms generated by the aluminum-lensed transducer were measured in degassed, filtered water with the

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