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● *Original Contribution*

HISTOTRIPSY LIQUEFACTION OF LARGE HEMATOMAS

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Abstract—Intra- and extra-muscular hematomas result from repetitive injury as well as sharp and blunt limb trauma. The clinical consequences can be serious, including debilitating pain and functional deficit. There are currently no short-term treatment options for large hematomas, only lengthy conservative treatment. The goal of this work was to evaluate the feasibility of a high intensity focused ultrasound (HIFU)-based technique, termed histotripsy, for rapid (within a clinically relevant timeframe of 15–20 min) liquefaction of large volume (up to 20 mL) extra-vascular hematomas for subsequent fine-needle aspiration. Experiments were performed using *in vitro* extravascular hematoma phantoms—fresh bovine blood poured into 50 mL molds and allowed to clot. The resulting phantoms were treated by boiling histotripsy (BH), cavitation histotripsy (CH) or a combination in a degassed water tank under ultrasound guidance. Two different transducers operating at 1 MHz and 1.5 MHz with f-number = 1 were used. The liquefied lysate was aspirated and analyzed by histology and sized in a Coulter Counter. The peak instantaneous power to achieve BH was lower than (at 1.5 MHz) or equal to (at 1 MHz) that which was required to initiate CH. Under the same exposure duration, BH-induced cavities were one and a half to two times larger than the CH-induced cavities, but the CH-induced cavities were more regularly shaped, facilitating easier aspiration. The lysates contained a small amount of debris larger than 70 μm, and 99% of particulates were smaller than 10 μm. A combination treatment of BH (for initial debulking) and CH (for liquefaction of small residual fragments) yielded 20 mL of lysate within 17.5 minutes of treatment and was found to be most optimal for liquefaction of large extravascular hematomas. (E-mail: tdk7@uw.edu)

Key Words: **High intensity focused ultrasound (HIFU), Histotripsy, Boiling histotripsy, Intramuscular hematoma, Compartment syndrome, Trauma, Thrombolysis, Fine needle aspiration.**

INTRODUCTION

Intramuscular hematomas are characterized by blood extravasation into the body of the muscle affected by trauma, with preserved integrity of the epimysium. Significant limb hematomas occur in diverse populations, from professional athletes to amateur runners and exercise enthusiasts who sustain muscle injuries from repetitive overuse, as well as sharp and blunt limb trauma (Conforti 2013). The main symptom related to the onset of an intramuscular hematoma is pain, which may be debilitating. There are currently no short-term treatment options for large hematomas; drainage is generally not possible because even large percutaneously placed drains are inefficient due to the firm gelatinous consistency of the hematomas. Conservative treatment includes rest, ice and compression, and the return to full activity is generally not possible before a period of 10–20 wk (Smith et al. 2006). In addition, post-traumatic myositis ossificans—calcification of muscle—occurs as a complication in approximately 20% of large hematomas. It is responsible for considerable morbidity, with symptoms of prolonged pain, diminished flexibility, local tenderness and stiffness lasting an average of 1.1 y. One of the most devastating sequelae of large intramuscular hematomas is extremity compartment syndrome (ECS), which occurs when muscle tissues take on excess fluid (moderate to large hematoma or muscle swelling due to inflammation) creating pressure that reduces blood flow and ischemic injury. Increased pressures can cause irreversible damage

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over time, resulting from loss of vascular perfusion leading to loss of limb function/viability, in some cases requiring amputation (Garner et al. 2014).

Clearly, a rapid definitive intervention aiming at evacuation of the space-occupying hematoma would reduce pain, improve function and avoid long term sequelae. Pulsed high intensity focused ultrasound (HIFU)-induced bubble activity could provide a means for such an intervention—non-invasive liquefaction of the hematoma followed by fine-needle aspiration. In fact, ultrasound is known to promote intravascular clot breakdown, as both a stand-alone procedure and used in conjunction with thrombolytic drugs and/or microbubbles (Birnbaum et al. 1998; Datta et al. 2008; Porter and Xie, 2001). Innumerable *in vitro* and *in vivo* studies have been conducted over the y, and acoustic cavitation is widely accepted as the dominant mechanism for mechanical disruption of the clot integrity and partial or complete recanalization of the vessel (Bader et al. 2015). Recently, a technique termed histotripsy has been demonstrated to be an efficient, non-invasive tool in dissolving large *in vitro* and *in vivo* vascular clots without thrombolytic drugs within 1.5–5 min into debris 98% of which were smaller than 5 microns (Maxwell et al. 2009, Maxwell et al. 2011a). The main challenge in the application of this same approach to the large extravascular hematomas is their large volume (20–50 mL) compared to the intravascular clots, which necessitates higher thrombolysis rates to complete the treatment within clinically relevant times (~15–20 min). On the other hand, the concerns regarding the size of the debris that can embolize into downstream vessels and the degree of hemolysis are not important compared with intravascular thrombus.

Thus, the main goal of this work was to evaluate the feasibility of using histotripsy to rapidly (within ~20 min) liquefy large extravascular hematomas for subsequent fine-needle aspiration. The treatment time frame limitation was chosen based on the review of the existing methods of soft tissue hematoma evacuation: drain placement, which averages 45–60 min (including preparation and post placement cleaning), and fasciotomy, which averages 30–45 min. It is preferred that the procedure can be performed in an outpatient setting, under regional anesthesia/sedation, which reinforces these time limits. Further extending the treatment time substantially increases the procedure costs and makes it less likely to become clinically adopted.

Two different histotripsy methods have been developed over the past decade: cavitation histotripsy (CH) and boiling histotripsy (BH) (Khokhlova et al. 2015). In BH, non-linear propagation effects on the way from the transducer to the focus lead to the formation of a shock front at the focus. Absorption and heating at the shock front is very large and leads to a highly localized temperature rise of over 100°C, resulting in a boiling vapor bubble in only a few milliseconds (Canney et al. 2010). The explosion of the millimeter-sized boiling bubble and its further interaction with the shocks causes localized mechanical erosion of tissue at the focus (Simon et al. 2012). If the ultrasound pulse does not significantly exceed the time-to-boil and the duty factor is low enough to avoid heat buildup (below 2%), thermal injury to tissue is negligible (Khokhlova et al. 2011; Wang et al. 2013). In CH, shorter (microsecond instead of millisecond) ultrasound pulses with higher pressure amplitude, repeated with low duty factor (less than 1%) periodically produce dense energetic bubble clouds in tissue. The activity of the bubble clouds mechanically disintegrates tissue in the focal area to a sub-cellular level (Maxwell et al. 2011b; Parsons et al. 2006).

Thus, both histotripsy techniques induce transient bubble activity in the focal area of the transducer and lead to the same outcome of tissue liquefaction. In both techniques, reliable treatment monitoring is achieved by B-mode ultrasound imaging of the highly reflective bubbles that appear as bright hyperechoic regions. Furthermore, both techniques have previously demonstrated advantageous tissue selectivity, both *in vivo* and *ex vivo*; for example, connective tissue structures *e.g.,* blood vessels, biliary structures or fascia surrounding muscle groups and organs, proved to be very resistant to mechanical damage and were largely unaffected by BH treatment while the more fragile cellular components were completely lysed (Khokhlova et al. 2014).

One notable difference that is relevant here is that the individual lesions produced by BH are larger than those produced by CH for the same treatment time, using the same ultrasound frequency. On the other hand, a unique feature of the CH technique is the formation of fluid vortices adjacent to the bubble cloud that were shown to attract, trap and erode millimeter-sized thrombus fragments if induced in a large blood vessel (Maxwell et al. 2014; Park et al. 2013). Thus, we hypothesized that a combination of BH (for large-scale debulking of a large hematoma) and CH (for eroding residual fragments) would optimize liquefaction treatment times for large extravascular hematomas. In this work CH, BH and a combination thereof were investigated in an *in vitro* model of a large hematoma in an effort to maximize the rate of thrombolysis for subsequent fine-needle aspiration.

MATERIALS AND METHODS

Experimental arrangement

All experiments were performed using an *in vitro* model of a large hematoma. Fresh bovine blood obtained from a local butcher was poured into plastic molds (50 mL per mold) and allowed to clot at room