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● *Original Contribution*

EFFECT OF FREQUENCY AND FOCAL SPACING ON TRANSCRANIAL HISTOTRIPSY CLOT LIQUEFACTION, USING ELECTRONIC FOCAL STEERING

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Abstract—This *in vitro* study investigated the effects of ultrasound frequency and focal spacing on blood clot liquefaction *via* transcranial histotripsy. Histotripsy pulses were delivered using two 256-element hemispherical transducers of different frequency (250 and 500 kHz) with 30-cm aperture diameters. A 4-cm diameter spherical volume of *in vitro* blood clot was treated through 3 excised human skullcaps by electronically steering the focus with frequency proportional focal spacing: $\lambda/2$, 2 $\lambda/3$ and λ with 50 pulses per location. The pulse repetition frequency across the volume was 200 Hz, corresponding to a duty cycle of 0.08% (250 kHz) and 0.04% (500 kHz) for each focal location. Skull heating during treatment was monitored. Liquefied clot was drained *via* catheter and syringe in the range of 6–59 mL in 0.9–42.4 min. The fastest rate was 16.6 mL/min. The best parameter combination was λ spacing at 500 kHz, which produced large liquefaction through 3 skullcaps (23.1 ± 4.0, 37.1 ± 16.9 and 25.4 ± 16.9 mL) with the fast rates (3.2 ± 0.6, 5.1 ± 2.3 and 3.5 ± 0.4 mL/min). The temperature rise through the 3 skullcaps remained below 4°C. (E-mail: tgerhard@umich.edu) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Histotripsy, Intra-cerebral hemorrhage, Hemorrhagic stroke, Electronic focal steering, Cavitation.**

INTRODUCTION

Intra-cerebral hemorrhage (ICH) accounts for 10%–15% of all strokes and affects approximately 2 million people worldwide (Go et al. 2013; Kulina et al. 2012; Qureshi et al. 2009). ICH is characterized by blood vessel rupture within the brain that leads to the formation of a blood clot therein. Because of its encasement by the skull, the formation of a blood clot within the brain causes an increase in intra-cranial pressure that can cause immediate injury to neurons and axons *via* mechanical distortion. In addition, the rise in intra-cranial pressure (ICP) and brain swelling leads to secondary injuries that can occur as the cerebral perfusion pressure decreases. The extent of the ICP increase is dependent on the size of the ICH and is a significant factor in patient outcome. Furthermore, delayed cerebral toxicity is caused by the degradation of remaining blood products. In general, patients diagnosed with ICH have a 30-d mortality rate of approximately 40% (Flaherty et al. 2006). Large clots (30–60 mL) are even more detrimental to patient outcome (Broderick et al. 1993, 1994; Dennis 2003; Flaherty et al. 2006). This necessitates a quick and effective evacuation procedure for blood clots formed within the brain. The mainstay treatment for ICH is surgical evacuation *via* a craniotomy. Craniotomy provides a quick access to evacuate clots; however, the procedure remains highly invasive as normal brain tissue may need to be traversed to remove the clots. In fact, craniotomy surgery leading to removal of ICH has not been shown to improve the functional outcome or reduce the morbidity and this lack of effectiveness may be related to the injury caused to surrounding cerebral tissue (Fernandes et al. 2000; Hankey and Hon 1997; Mendelow et al. 2005, 2013).

Minimally invasive clot evacuation techniques have been developed to overcome the issues associated with craniotomy-based surgeries. Specifically, techniques using a catheter inserted through a small hole in the skull

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to deliver thrombolytic drugs, such as recombinant tissue plasminogen activator (rt-PA), to liquefy clots and aspirate the liquefied volume have been investigated. However, because of the slow perfusion of the thrombolytic drugs into the clot, the treatment typically takes 3–7 d with the catheter within the ICH for the entire duration, thus requiring a lengthy intensive care unit (ICU) stay. These techniques are currently undergoing clinical investigation with early results revealing an ability to reduce clot size, as well as ICH-related edema (Hattori et al. 2006; Morgan et al. 2008; Wang et al. 2009). However, the functional outcome of ICH survivors has not improved, likely because of the long treatment time required to liquefy and aspirate the volume. Additionally, although such techniques have reported up to a 50% reduction in clot size, this may be insufficient for large clots, where a greater reduction may be necessary, causing treatment times to exceed what is clinically feasible (*i.e.,* >7 d). For smaller clots typical of ischemic stroke, thrombolytic drugs, such as rt-PA, have been administered with and without contrast agent microbubbles and clots have been insonated with low-amplitude ultrasound pulses to increase the efficacy and rate of clot liquefaction (Alexandrov et al. 2004; Alexandrov et al. 2008; Datta et al. 2006; Hitchcock and Holland 2010; Holland et al. 2008; Meairs et al. 2012). The combination of microbubbles and ultrasound has shown improved penetration of thrombolytic drugs into clots (Datta et al. 2008). Although such increased penetration may be sufficient for treating smaller clots found with ischemic stroke, the penetration depth may still be a limiting factor for larger clots typical of ICH.

High-intensity focused ultrasound (HIFU) techniques have been investigated for various brain applications. Magnetic resonance guided focused ultrasound (MRgFUS) is one technique that uses a thermal mechanism to deliberately kill tissue at a precise focal point and magnetic resonance imaging (MRI) to correct for the acoustic aberration and monitor the efficacy of the treatment. MRgFUS has established itself as a transcranial therapy and has had success in treating single spots in the brain for movement disorders such as essential tremor (Elias et al. 2013a, 2013b). MRgFUS has also been used to enhance drug delivery through the blood–brain barrier for treatment of brain tumors (Hynynen et al. 2006a; Nance et al, 2014; O'Reilly and Hynynen 2012). In addition, MRgFUS has been shown to thermally lyse clots through the skull in animal and human cadaver studies by increasing the temperature of the target clot by approximately 6°C, which is thought to cause mechanical breakdown of the clot *via* inertial cavitation (Monteith et al. 2013a, 2013b). The resulting liquid can then be aspirated out with a drainage catheter inserted through a bur hole in the skull. This provides a minimally invasive alternative for ICH treatment that does not use thrombolytic drugs and provides much faster liquefaction than the current clinical treatments. However, as a result of skull overheating caused by the applied ultrasound (≥100 μs at 10% duty cycle), MRgFUS has not been able to treat clots greater than 40 mL or regions within 2 cm of the skull, thus excluding ~80% of the brain cortex region where clots can form (Monteith et al. 2013a, 2013c; Ramanan and Shankar 2013; Wright et al. 2012). Additionally, although MRgFUS has shown the capacity to accelerate clot reduction time (3 h to liquefy up to 40 mL), the treatment time is still long relative to that needed for critical cases (*i.e.,* patients with clots greater than 60 mL).

Histotripsy is another focused ultrasound technology currently being developed for ICH treatment. Histotripsy uses short (≤2 cycles or ≤4 μs at 500 kHz), high energy pulses at a very low duty cycle (<0.1%) to generate cavitation microbubble clouds transcranially, using the intrinsic threshold method. In this method, cavitation is generated with the peak-negative pressure directly exceeding the threshold intrinsic to the target media to excite the pre-existing nuclei in the target tissue (Roberts et al. 2006; Xu et al. 2004, 2005, 2010). In water-based tissues such as clots this threshold is about 27 MPa with little change expected at various frequencies (Maxwell et al. 2013; Vlaisavljevich et al. 2015a, 2015b). The rapid and energetic bubble expansion and collapse of cavitation create high stress and strain in the clot at the focus that fractionates it into an acellular homogenate (Lin et al. 2014). In contrast to other FUS techniques, the tissue destruction caused by histotripsy has been shown to be purely mechanical, with negligible thermal effects (Kieran et al. 2007). Histotripsy clot liquefaction has been demonstrated in deep vein thrombosis model both *in vitro* and *in vivo* (Maxwell et al. 2009, 2011). Recently, histotripsy and boiling histotripsy have been used for treatment in an *in vitro* large extravascular hematoma model (Khokhlova et al. 2016). Additionally, the *in vitro* feasibility of histotripsy as a transcranial therapy for brain tissue has been investigated (Kim et al. 2014a; Sukovich et al. 2016).

Similar to MRgFUS, histotripsy can be used to liquefy clot through the skull, and the liquefied clot volume can be drained *via* a catheter inserted into the clot through a small bur hole. By using extremely short pulses (microsecond duration) and a low duty cycle (≤0.1%) to minimize skull heating, we hypothesize that histotripsy can overcome the limitations of MRgFUS to accelerate the treatment speed, widen the treatment location range to regions closer to the skull surface and liquefy clots larger than 40 mL.

In this paper, the use of histotripsy with electronic focal steering for fast transcranial clot liquefaction is