Trans-Fontanelle Ultrasound Guided Histotripsy for Intraventricular Clot Lysis in Neonatal Head Phantoms

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At-a-glance:

Trans-fontanelle Ultrasound guided Focused Ultrasound (USgFUS) is an effective means of non-invasive clot lysis in neonatal skull and brain phantom models.

Introduction

- Intraventricular hemorrhage (IVH) occurs in 3% of all live births in Canada, corresponding to 30% of neonates admitted to the neonatal intensive care unit (NICU) each year[1,2].
- Current treatments are invasive and are often ineffective in alleviating the clot burden[3].
- Complications due to IVH develop quickly, and infants, particularly those with very low birth weights often succumb to the condition[3].
- There is an unmet clinical need to develop and test non-invasive methods to dissolve IVH clots.
- Our group is proposing USgFUS can be an effective way to non-invasively dissolve these clots.

Objective

The objective of this study is to characterize trans-fontanelle ultrasound-guided histotripsy as a feasible method for clot lysis within neonatal brain ventricles.

Methods

Neonatal Head Phantom

- A thermosensitive gel was formulated to match the acoustic properties of neonatal brains[4] (Table 1).
- This gel was cast into a neonatal skull phantom from *True Phantom Solutions Inc*, and a porcine blood clot was formed within the phantom.
- The speed of sound and attenuation at 1Mhz was found to be 1554.3 ± 16.4 m/s and 2.7 ± 0.34 Np/m respectively.
- The values for speed of sound and attenuation are within the range listed for neonatal brain matter found in literature[4].

Substance	Amount	
Degasses DI Water	73.10%	[v/v]
Acrylamide/Bis-acrylamide 40% (w/v)	24.80%	[v/v]
Bovine Serum Albumin	15.00%	[w/v]
MB60°C (Thermochromic Magenta Ink)	2.00%	[v/v]
Silicon Dioxide (SiO2)	2.00%	[v/v]
Ammonium Persulfate (APS)	0.50%	[w/v]
TEMED	0.10%	[v/v]

Table 1: Formulation for Brain Phantom Gel

Clot Lysis Measurement

- To measure the amount of clot that was lysed, pre- and post-treatment MRIs (T1-W, T2-W and BFFE) were taken of the phantom.
- The clot volume was then measured by manually segmenting the images in 3D slicer.

USgFUS System

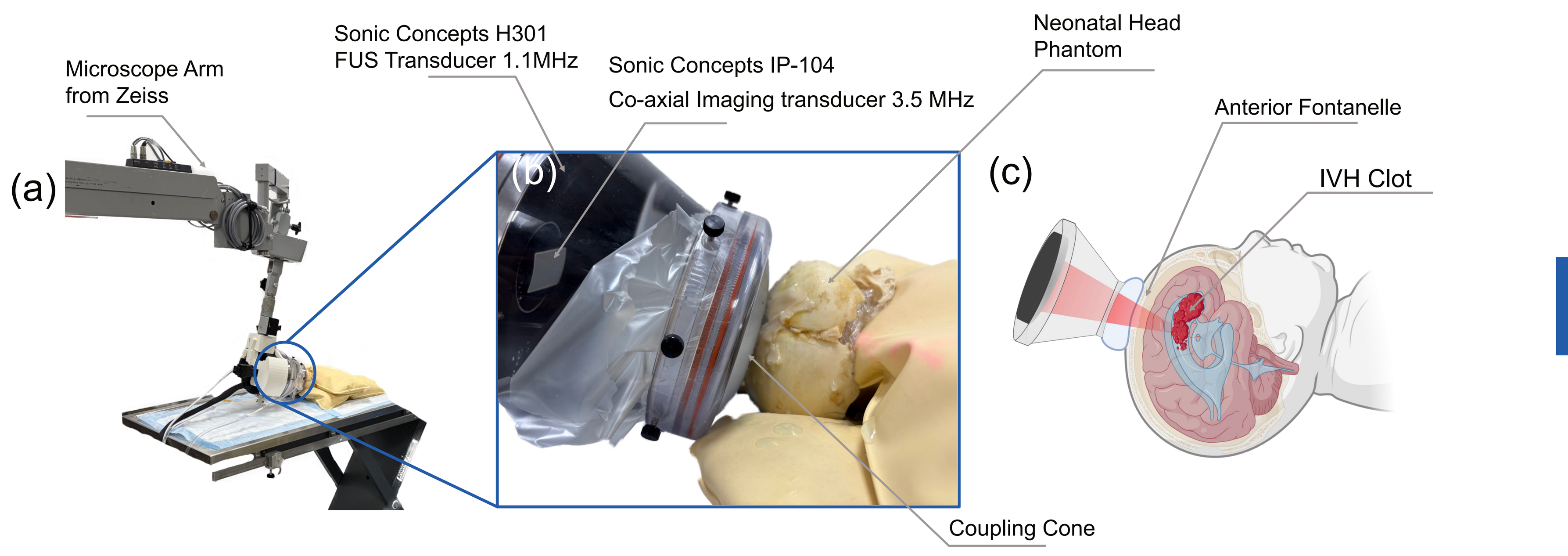

Figure 1: USgFUS system used for trans-fontanelle clot lysis. Not depicted here is the beamformer, the Vantage System from Verasonics, Inc. (a) The set up including the surgical table and surgical microscope arm being used to position the transducer over the phantoms fontanelle. (b) A zoomed in section showing the phantom model, and how the coupling cone interfaces with the phantom. (c) A diagram showing the location of the clot with respect to the fontanelle and the transducer.

FUS Parameter Characterization

- A 1.1MHz, 60 second pulsed sonication was applied with a 10 msec pulse duration and a 1.0 Hz pulse repetition frequency (PRF); the power was ramped up until clot lysis was observed (max 1645 w of electrical power) corresponding to 5 MPa peak negative pressure.
- These sonication parameters are consistent with boiling histotripsy.

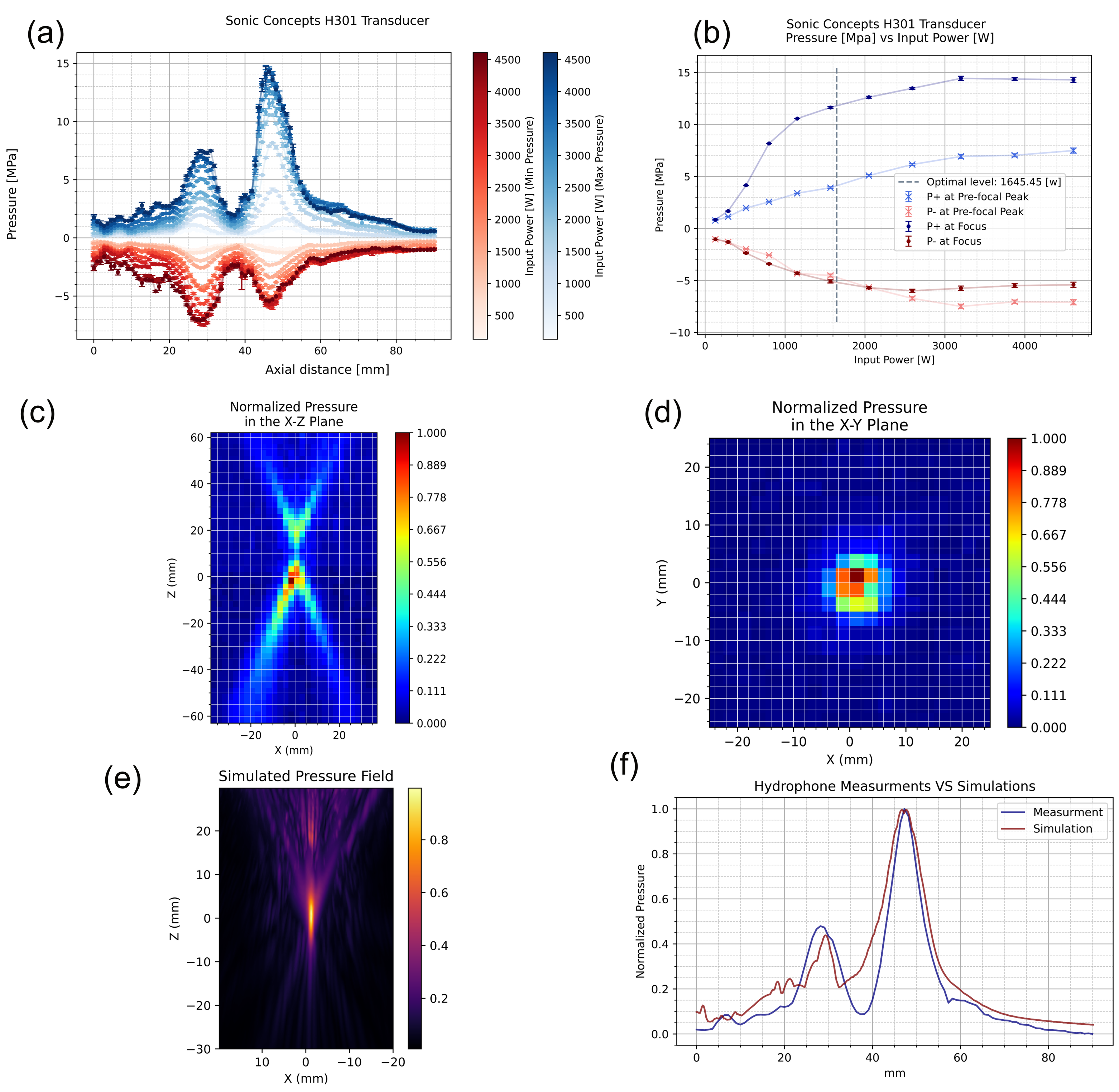

Figure 2: (a) Axial pressure plots for input powers ranging from 128 W to 4608 W, (b) Pressure (peck positive and negative) at the focus, and the prefocal peak over the input power range of 128 W to 4608 W. (c) X-Z normalized pressure beam profile through the focus. (d) X-Y normalized pressure beam profile through the focus. (e) Simulated X-Z pressure beam profile. (f) Axial beam plot comparing normalized pressure to simulated data. All hydrophone measurements were taken with the Precision Acoustics fibre optic hydrophone.

Results

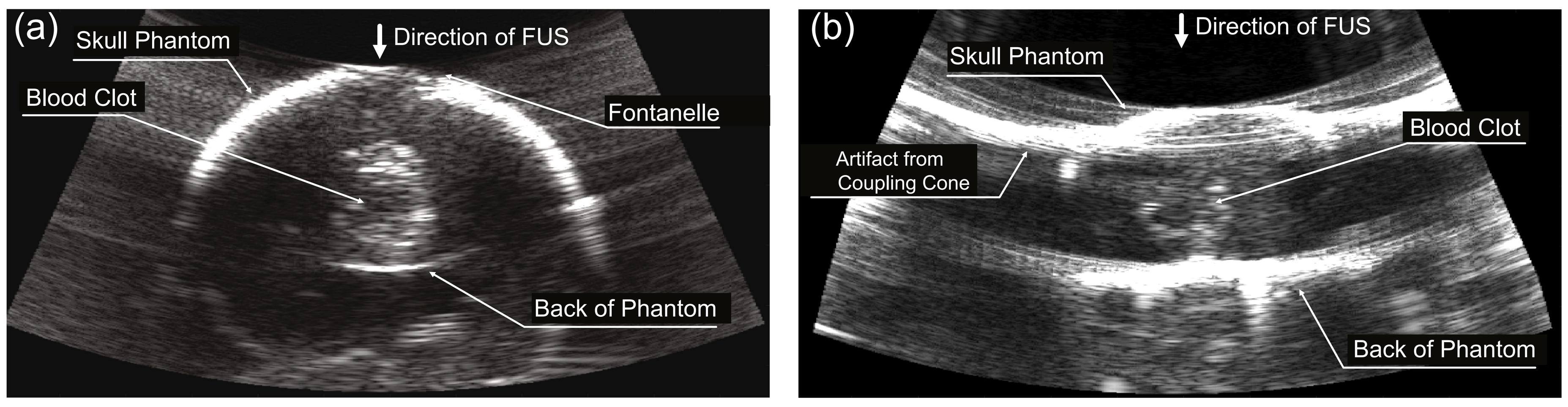

Figure 3: Intra-treatment ultrasound Images of the neonatal head phantom, taken with the IP-104 ultrasound transducer. (a) Taken using a water tank as the coupling medium, with the phantom completely submerged in de-gassed de-ionized water. (b) Taken using the coupling cone and water bag as the coupling medium.

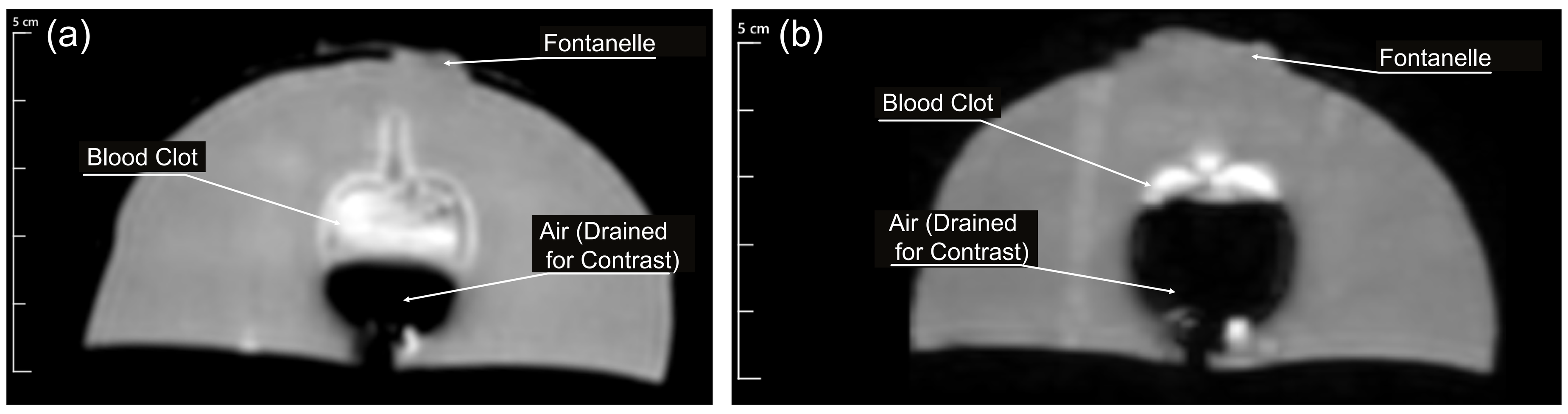

Figure 4: Pre- and post-treatment T1 MR images of the skull and brain phantom, with the fluid backing the clot removed before and following clot lysis to increase contrast for segmentation. (a) Pre-treatment MRI. (b) Post-treatment MRI.

Figure 5: (a) The effect of the two coupling methods used had on ultrasound-mediated clot lysis. (b) The effect of the clot age on ultrasound-mediated clot lysis for clots <5hrs and >12hrs. (c) The effect of the skull on ultrasound-mediated clot lysis within the phantom models. Both groups used the treatment cone as the coupling medium.

Discussion

Intra-treatment Images

- With the current system, we can only image once per pulse, so our imaging temporal resolution is limited to the PRF of the solicitations (1/sec).
- The blood clots are clearly visible in the intra-treatment images, but higher frequency imaging may lead to higher spatial resolution and improved contrast at clot margins.
- Work investigating different coupling methods and media may lead to better images, and clot lysis.

Effect of clot age

- There was no significant effect on the percentage of clot lysis between clots <5hrs old and >12hrs.

Effect of coupling method

- Future work should investigate the use of different membrane material and other coupling methods that may yield better results, and limit artifacts from membrane (Figure 3b).
- Even with the coupling cone there is still a significant amount of clot lysis ($p=0.03$).

Effect of the skull

- Boiling histotripsy is highly effective 90.2% ± 0.06% (Figure 5c). This is in agreement with past studies using similar ultrasound parameters with different transducers[5].
- This study also showed the skull has a significant effect of clot lysis. Reducing the percentage of clot lysis down to 27.5% ± 0.09% (p=8.7e-6).
- The skull phantom used has similar properties to the skull but is 100% thicker than real neonatal skulls due to manufacturing limitations, making the attenuation of the phantom very high.
- The acoustic propagation across the skull phantom is significantly reduced compared to real neonatal skulls. It is our view this study represents the "worst case" scenario for propagation across the skull.

Conclusion

- Trans-fontanelle ultrasound-guided histotripsy is a feasible method for clot lysis within neonatal brain ventricles.
- These phantoms represent a worse case scenario attenuating skull when compared to real neonatal skulls, and significant clot lysis was still achievable across the phantom's skull.
- Future work investigating more efficient coupling may improve clot lysis further.

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