The Effect of Pulse Length on Opening Volume and Reversibility of Theranostic Ultrasound-Mediated Blood-Brain Barrier Opening in Vivo

Alec J. Batts[1], Robin Ji[1], Rebecca L. Noel[1], and Elisa E. Konofagou[1,2], [1]Department of Biomedical Engineering, [2]Department of Radiology, Columbia University, New York, USA

Background, Motivation and Objective

Blood-brain barrier opening (BBBO) with theranostic ultrasound (TUS) is a novel modality for synchronous BBBO using short pulses and power cavitation imaging (PCI) with a single phased array (Ji *et al*., IUS 2019). While our group has demonstrated initial feasibility of TUS-mediated BBBO *in vivo*, the effect of TUS pulse length on BBBO volume, BBB closure, and PCI signal intensity remains to be elucidated.

Statement of Contribution/Methods

A P4-1 phased array (ATL, Philips) was operated at a frequency of 1.5 MHz by a Verasonics research ultrasound system (Vantage 256) to perform synchronous bilateral BBBO and PCI in C57BL/6J mice (1.0 MPa derated PNP, 8×10^8 microbubbles (MBs)/mL, 35 mm focal depth, ±3.72° steering angle). Separate transmit sequences were employed for each hemisphere by interleaving 100 sets of electronically steered and focused transmits acquired at a PRF of 1000 Hz with odd numbered transmits deploying a distinct pulse length and negative steering angle from that of even numbered transmits. This sequence was repeated at a burst repetition frequency of ~0.33 Hz over a sonication duration of 2 minutes enabling comparison of multiple pulse lengths within the same animal with a single bolus injection of MBs. Peak and total PCI signal intensity for each sonication was defined as the maximum signal intensity after MB injection, and the summed signal intensity within a 24 mm^2 ROI surrounding the focal point over all frames, respectively.

Results/Discussion

An increase in BBBO volume was observed with increasing pulse length (Fig. 1A), along with a linear correlation ($R^2 = 0.49$) between BBBO volume and pulse length (Fig. 1E). Peak PCI signal intensity (Fig. 1B) and total PCI signal intensity (Fig. 1C) increases were also observed, along with a linearly correlated relationship between PCI signal intensity and TUS pulse length (Fig. 1F). BBBO volume was quantified for each pulse length over a period of 72 hours to determine the reversibility of TUS-mediated BBBO with varying pulse lengths. Seven hours after TUS exposure, a 99.5%, 96.3% and 81.2% reduction in BBBO volume was observed for 1.5-cycle, 5-cycle, and 10-cycle sonications, respectively (Fig. 1D). The BBBOs for 1.5-cycle, 5-cycle and 10-cycle sonications were considered predominantly closed after 7, 24, and 72 hours, respectively, as confirmed by contrast enhanced T_1-weighted MRI (Fig. 1G). These results indicate that the volume and reversibility of BBBOs achieved with TUS in the same animal may be mediated by pulse length and predicted by PCI signal intensity.

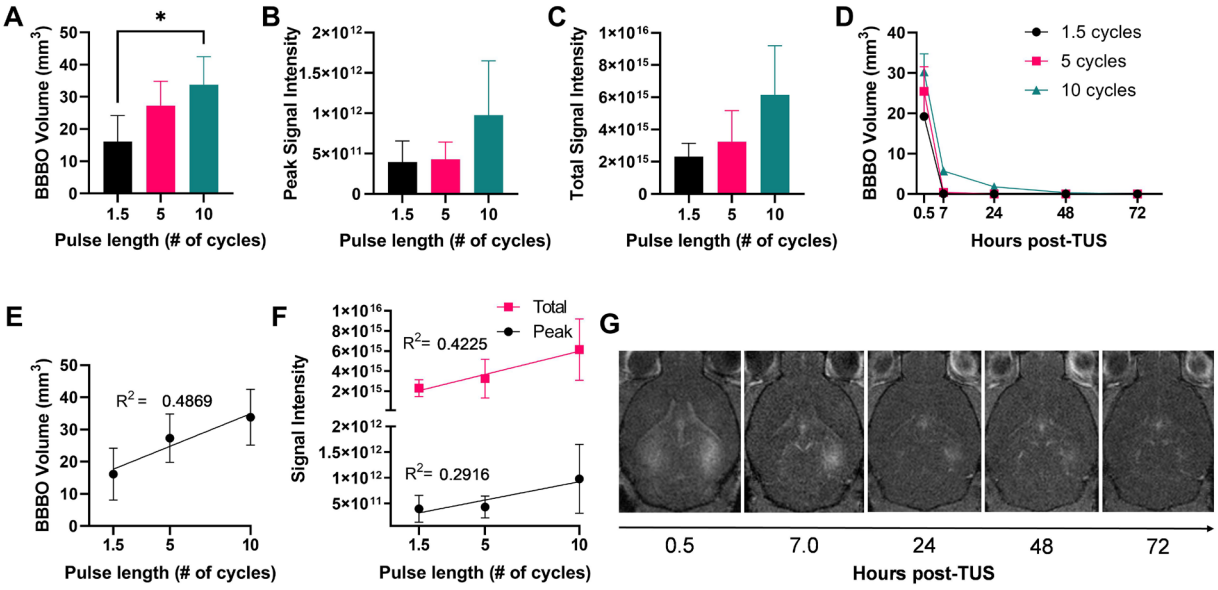

Fig. 1: (A) Increase in BBBO volume with pulse length. *p<0.05 determined by one-way ANOVA and post-hoc Tukey's multiple comparisons test (n=4). Increase in PCI **(B)** peak signal intensity and **(C)** total signal intensity with increasing pulse length. **(D)** Reversibility of BBBO volume after TUS (n=2). **(E)** Linear correlation between BBBO volume and pulse length determined by standard linear regression. **(F)** Linear correlation between PCI signal intensity and pulse length. **(G)** Representative contrast-enhanced T_1-weighted MRIs depicting BBB closure over time (10-cycle sonication on right hemisphere, 1.5-cycle sonication on left hemisphere). All error bars denote the sample mean ± standard deviation.