

Half-year Progress Report

Project Title: Image-guided Non-invasive Ultrasonic Thrombolysis Using Histotripsy

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12/9/2013 – 3/31/2015

• Summary of Progress

Histotripsy, a novel, non-invasive therapeutic technique, employs controlled pulsed cavitation ultrasound for tissue ablation and is currently being evaluated for thrombolysis and palliation of congenital heart disease. Some forms of therapeutic ultrasound cause intravascular hemolysis. Hemolysis due to histotripsy has not been previously evaluated. This study aimed to investigate the extent and consequences of hemolysis caused by histotripsy in vivo.

Free flowing blood in the porcine femoral vein was treated with histotripsy therapy in 11 animals with systemic heparinization and 11 animals without heparin. Serum and hemodynamic measurements were obtained at baseline (0), 2, 5, 10, 15, and 30 min, as well as 48-72 hours post-procedure. Of the 11 non-heparin treated animals, 5 died during or immediately following Histotripsy, while all animals in the heparin group survived (non-heparin group mortality 45% vs. heparin group mortality 0%, $p < 0.05$). Among all animals, serum hematocrit decreased slightly following histotripsy (32.5 ± 3.6 to $29.4 \pm 4.2\%$, $p < 0.001$). There was a significant increase in free hemoglobin (6.2 ± 4.6 to 348 ± 100 mg/dL, $p < 0.001$) and LDH (365 ± 68 to 722 ± 85 U/L, $p < 0.001$). Right ventricle systolic pressure (RVSP) also increased (23.2 ± 7.2 to 39.7 ± 12 mmHg, $p < 0.001$). After 48 to 72 hours, hematocrit remained slightly decreased, and LDH remained slightly increased, compared to baseline, though free hemoglobin nearly returned to baseline. These results show that histotripsy applied to the circulating blood volume is associated with high mortality in non-heparinized animals, but is generally safe with systemic heparinization. A transient increase in free hemoglobin was observed with no clinically significant reduction in total hematocrit. There is also a transient increase in RVSP.

• Publications

Published and In Press

Zhang X, Miller RM, Lin KW, Levin AM, Owens GE, Gurm HS, Cain CA, Xu Z. Real-time Feedback of Histotripsy Thrombolysis Using Bubble-induced Color Doppler. *Ultrasound Med Biol*. In Press.

In Review

Vlaisavljevich E, Lin K-W, Maxwell A, Warnez M, Mancina L, Singh R, Putnam AJ, Fowlkes JB, Johnsen E, Cain CA, Xu Z. Effects of Ultrasound Frequency and Tissue Stiffness on the Histotripsy Intrinsic Threshold for Cavitation. *Ultrasound Med Biol*. In Review.

Vlaisavljevich E, Lin K-W, Warnez M, Singh R, Mancina L, Putnam A, Johnsen E, Cain CA, Xu Z. Effects of tissue stiffness and ultrasound frequency on histotripsy-induced cavitation bubble behavior. *Physics in Medicine & Biology*. In review.

In Preparation

Devanagondi R, Zhang X, Owens GE, Gurm HS, Levin AM, Xu Z. The hemodynamic and hematological effects of histotripsy. In preparation.

Presentations

1. Devanagondi R, Zhang X, Owens GE, Gurm HS, Levin AM, Xu Z, editors. The hemodynamic and hematological effects of histotripsy. In preparation. Focused Ultrasound Symposium; 2014 Oct 12-16; North Bethesda, MD.
2. Zhang X, Miller RM, Maxwell AD, Cain CA, **Xu Z**. Real-time Feedback of Histotripsy Thrombolysis using Bubble-induced Color Doppler. IEEE International Ultrasonics Symposium; 2014 Sep 3-6; Chicago, IL, USA.
3. Vlaisavljevich E, Warnez M, Singh R, Putnam A, Cain C, **Xu Z**. Response of Soft Tissue to Pulsed Cavitation Ultrasound Therapy – Histotripsy Paper presented at: National Congress on Theoretical and Applied Mechanics; June 15-20, 2014; Lansing, MI, USA.
4. Vlaisavljevich E, Warnez M, Johnsen E, Putnam A, Cain CA, **Xu Z**, Investigation of the Role of Tissue Mechanical Properties and Ultrasound Frequency in Histotripsy-induced Cavitation. International Symposium on Therapeutic Ultrasound; Apr 2-5, 2014, Las Vegas, NV, USA.
5. Devanagondi R, Xu Z, Zhang X, Ives K, Gurm H, Owens GE, editors. The hemodynamic and hematological effects of Histotripsy The Society for Cardiovascular and Angiography and Interventions Scientific Sessions; 2014 May 28-31; Las Vegas, NV.

• Follow-on Funding

Grant Title: Image-guided non-invasive Ultrasonic Thrombolysis Using Histotripsy

Grantor: NIH

Funding Mechanism: R01 renewal

Amount: \$2,032,190.00 (all to U of Michigan)

Funding Period: 7/1/2014 - 6/30/2018

Notes:

This R01 renewal covers many aspects of the clinical translation of histotripsy for DVT and technical advancements to expand histotripsy thrombolysis for other applications.