High-intensity focused ultrasound (HIFU) for dissolution of clots in a rabbit model of embolic stroke

Alison Burgess[1], Yuexi Huang[1], David Goertz[1,2], and Kullervo Hynynen[1,2]

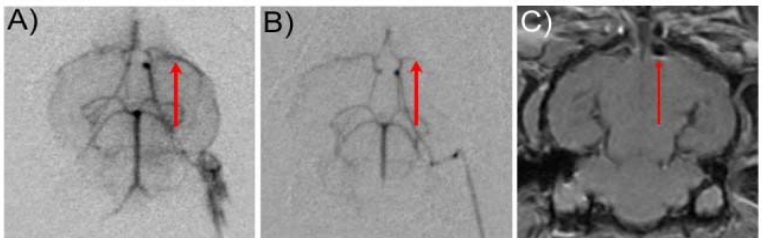
[1]*Physical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada,* [2]*Medical Biophysics, University of Toronto, Toronto, Ontario, Canada*

Problem:

Intravenous delivery of the thrombolytic agent, tissue plasminogen activator (tPA), is the primary medical intervention for acute ischemic stroke. tPA can be effective for a subset of patients however it is not administered to many patients due to the potentially serious side effects.[1] High-intensity focused ultrasound (HIFU) has recently been shown to cause clot dissolution in thrombosed femoral arteries.[2,3] Here, we demonstrate that HIFU is feasible for thrombolysis in a model of ischemic stroke and may serve as an alternative to tPA treatment.

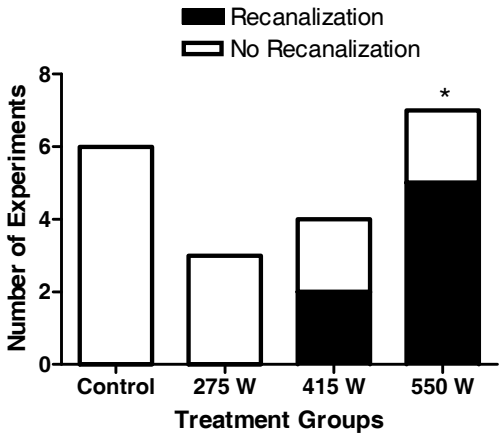
Methods:

We developed an embolic model of ischemic stroke in New Zealand white rabbits. 14 days prior to HIFU treatment, a craniotomy was performed to ensure proper ultrasound wave propagation. Briefly, a piece of bone (2 x 4 cm) was removed from the parietal skull leaving the dura intact. The skin was sutured over top and the animal was recovered. On the experiment day, rabbits were embolized through the internal carotid artery with arterial blood clots containing superparamagnetic iron oxide. Angiography was used to confirm blockages in blood flow. The rabbits were then placed on the HIFU positioning system inside a 3.0T MRI. T2* and time of flight imaging were used to locate the iron-loaded blood clot and to precisely target the HIFU beam. A 1.5 MHz single element transducer was used to sonicate the blood clot (275-550 W, 1 ms bursts, 20 s, 0.1% duty cycle) through the cranial window. Following sonication, post-treatment MR images and angiograms were obtained to determine whether flow was restored.



Results:

Using this model of embolic stroke, we caused reproducible blockages of the proximal middle cerebral artery (MCA) as determined by angiography (Panel A, B). This was confirmed by identification of the iron-loaded clot on TOF-MRI (Panel C). 1 hr after clot injection, the animals received HIFU treatment using powers ranging from 275-550 W. No recanalization was observed in control, untreated animals. In 2 of 4 animals (50%), partial or full recanalization was achieved with 415W. When the power was increased to 550W, partial or full recanalization was achieved in 5 of 7 animals (71%, graph). Histological analysis indicated the blocked vessels were still intact following sonication. However, minor red cell extravasations at the site of sonication were observed. Survival experiments evaluating the impact of the treatment on stroke pathology are currently underway and have shown promising initial results.



Conclusions:

These results demonstrate the feasibility of using HIFU, as a stand-alone method, for effective thrombolysis *in vivo*. HIFU, combined with imaging modalities used to identify and assess stroke patients, could dramatically reduce the time to achieve flow restoration in patients thereby significantly increasing the number of patients which benefit from thrombolysis treatments.

References:

1) The National Institute of Neurological Disorders and Stroke rTPA Stroke Study Group (1995) N Eng J Med 333: 1581–1587. 2) Wright C, Hynynen K, Goertz DE (2012) Investigative Radiol 47: 217–225. 3) Maxwell AD, Cain CA, Duryea AP, Yuan L, Gurm HS, et al. (2009) Ultrasound Med Biol 35: 1982–1994.