Quantitative Relaxation Time and Susceptibility Mapping of Thrombus

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Target Audience: Researchers and clinicians interested in thrombus MRI.

Purpose: Heart attack and stroke are the leading causes of death and disability in the US In most instances, these devastating cardiovascular events are triggered by the formation and breakage of a blood clot (thrombus), which is subsequently lodged within an artery supplying the heart or brain. The composition and structural stability of a thrombus as it develops over time has been increasingly recognized as a crucial factor in predicting outcomes and guiding treatments. While MRI is used to detect the presence of thrombi[1], there is a limited knowledge on the longitudinal progression of their MR properties. Recent works have studied the effect of thrombus age on T1, T2 and diffusion weighted images using an animal model[2,3]. However quantitative measurements were not obtained. Here, we design and construct an in vitro flow-driven thrombus model and use quantitative MR methods to study changes in its magnetic susceptibility and relaxation times (T1, T2) with histological findings.

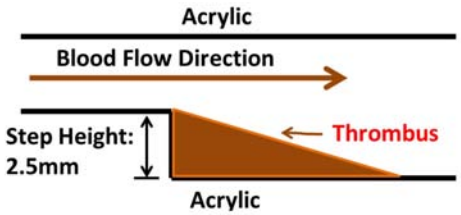

Figure 1: Illustration of backward-facing step model design.

Methods: A backward-facing step model (200 mm long acrylic tube with a 2.5 mm step and a 10 mm downstream diameter) was placed into a flow loop driven by a peristaltic pump to create a thrombus (Fig.1) and cleansed by phosphate buffered saline (PBS). 450 ml bovine blood was drawn from the jugular vein with citrate phosphate dextrose adenine (CPDA) solution as an anti-coagulant, and was recalcified with a 6.45% calcium chloride ($CaCl_2$) solution to reverse the effects of the CPDA using a volume ratio of 2% to blood. The blood was circulated (0.2 m/s and upstream Reynolds number of 490) for a predetermined period of time (1 and 12 hours) at room temperature. The thrombi were gently removed with forceps, placed into a petri dish filled with paraformaldehyde, refrigerated before embedded in 1% agar, and then imaged on a 7T Bruker scanner. After MRI scanning, fibrin staining (using Carstairs' method with 45 min picric acid orange and 30 min aniline blue) was performed on the center slice of the thrombi.

The imaging parameters were: 1) Quantitative susceptibility mapping (QSM): 3D multi-echo gradient echo, TR=44.5 ms, first TE=3.8 ms, echo spacing=5.1 ms, voxel size=0.1x0.1x0.1 mm^3, number of averages=14; 2) T1 mapping: 2D progressive saturation spin echo, TR=6000, 4000, 2000, 1000, 500, 100 ms, TE=11 ms, voxel size=0.1x0.1x0.5 mm^3, number of averages=3; 3) T2 mapping: CPMG multi-echo spin echo, TR=3 s, number of echoes=32, echo spacing=10.8 ms, voxel size=0.1x0.1x0.5 mm^3, number of averages=12. Susceptibility maps were obtained using the Morphology Enabled Dipole Inversion (MEDI) algorithm[4]. T1 and T2 maps were extracted using a three-parameter exponential signal model and the Levenberg-Marquardt algorithm. In addition, the volume of each thrombus was measured on the gradient echo magnitude images.

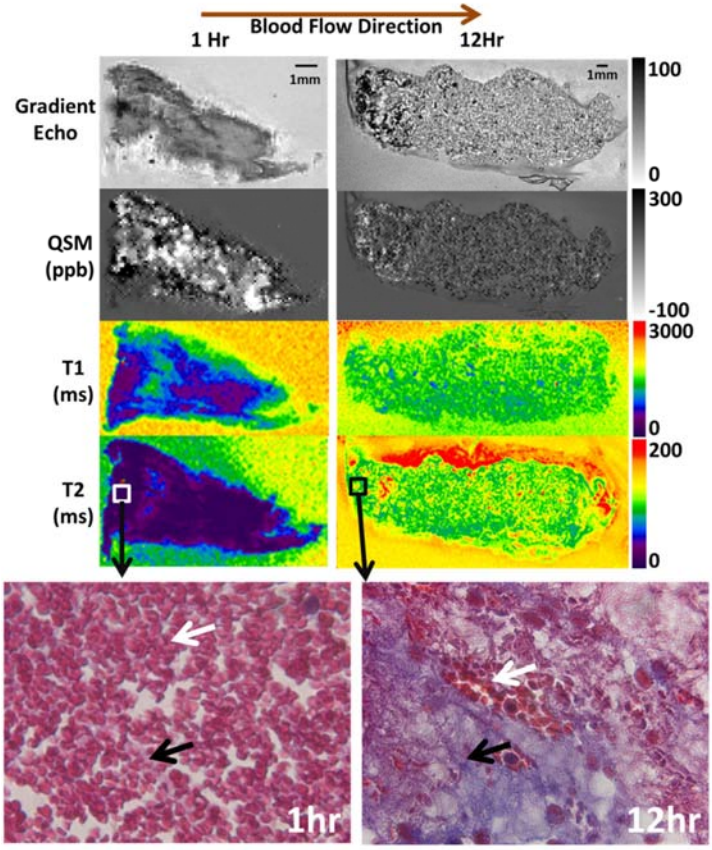

Figure 2: Images of gradient echo magnitude, QSM, T1, T2 mapping, and histology images of 1hr and 12hr thrombi. In histology images, red blood cells appear red (white arrow). Fibrins appear blue (black arrow).

Results: Figure 2 shows the T1, T2 and QSM maps for the 1 hour and 12 hour thrombi, demonstrating an approximate two-fold increase in T1 and an approximate ten-fold increase in T2, while the susceptibility changed from strongly paramagnetic to slightly diamagnetic (Table 1). The volume of the thrombus increased from 20mm^3 at 1 hour to 245mm^3 at 12 hour. Figure 2 also shows an example of histology images obtained for a center slice at the step.

Table 1: ROI measurements of QSM, T1 and T2 mapping of 1hr and 12hr thrombus (Mean ± std).

	Volume (mm^3)	Susceptibility (ppb)	T1 (ms)	T2 (ms)
1 Hr	19.7	72 ± 83	670 ± 162	11 ±3
12 Hr	245	-1.5 ± 37	1425 ± 179	108 ± 19

Discussion: From 1 hr to 12 hr thrombus, the observed decrease of susceptibility (73.5 ppb) may suggest the loss of red blood cells (RBCs) that contain paramagnetic iron (deoxyhemoglobin (dHb) or metahemoglobin) and an increase in diamagnetic fibrin structure. The 1425ms T1 and 108ms T2 at 12hr are normal relaxation values for blood, consistent with the slightly diamagnetic -1.5ppb and suggesting depletion of RBCs of paramagnetic iron. The 670ms T1 and 11ms T2 resembles that of acute hemorrhage where RBCs contain paramagnetic dHb (strong T2 shortening, high susceptibility 72ppb) and have intact membrane (slight T1 shortening). This MRI data interpretation is supported by histology showing most RBCs were gone by 12hr with substantial fibrin structures buildup.

CONCLUSION: We have demonstrated the feasibility of an in vitro thrombus model to study thrombus formation and progression under flow conditions. Our preliminary results indicate that the dynamic changes in thrombus can be measured by quantitative relaxation time mapping and quantitative susceptibility mapping using MRI, which may be used to predict the age, composition and structural stability. The effect of flow rate, step height, and circulation time will be investigated in future work.

Reference: 1). Samm, T., et al., Radiology, 2007. 244(1): p.64-77. 2). Fujimoto, M., et al., Stroke, 2013. 44(5): p.1463-5. 3). Ichiki, M., et al., Br J Radiol, 2012. 85(1012): p. 331-8. 4). Liu, T., et al., MRM, 2011. 66(3): p. 777-83.