Estimation of Red Blood Cell Flow using Microbubbles as a Contrast Agent for DSC-MRI

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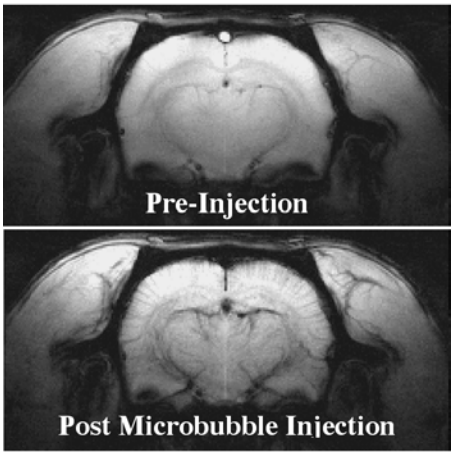
Introduction: Commonly used DSC-MRI contrast agents are distributed into blood plasma and as such provide hemodynamic parameters related to plasma flow and plasma volume. In this study we evaluate the use of gas-filled, encapsulated microbubbles, commonly used for ultrasonic imaging, as an intravascular *first pass* susceptibility contrast agent for DSC-MRI at high fields. Previous MRI studies have demonstrated the potential of detecting microbubble induced susceptibility variations (1,2). Microbubbles have a diameter and vascular distribution similar to that of red blood cells (RBC)s making them an attractive contrast agent to evaluate RBC flow in normal and pathological tissue (3). The effective lifetime of microbubbles in the blood stream is less than 10 minutes allowing for repeat injections without the potential of saturating the MRI signal intensity. The purpose of this study was to evaluate the potential of microbubbles as a first pass contrast agent in normal rat brain tissue and compare their contrast kinetics to that of the iron oxide plasma agent ferumoxytol.

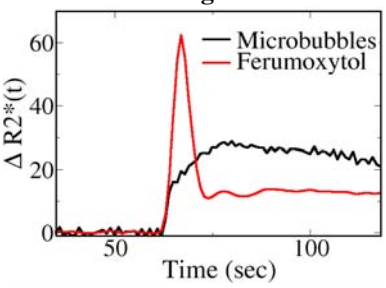
Methods: Dynamic susceptibility contrast MRI studies using microbubbles (Definity, Bristol-Myers Squibb Medical Imaging, North Billerica, MA) and ferumoxytol (Advanced Magnetics, Cambridge MA) have been performed on 12 normal rats using a Varian 9.4T scanner. A 3-minute GE EPI pulse sequence (TR/TE = 250 ms/6 ms, 4 shots 1/2 k-space, 3 slices, slice thickness = 2 mm, FOV = 32 mm x 32 mm, matrix = 64 x 64) was used for each dynamic scan. At 1 minute into the first scan, a 333 µL/kg bolus of undiluted microbubble was administered through the jugular vein (n = 9) or the common carotid artery (n = 3). Ten minutes after the first scan this procedure was repeated using 3 mg/kg of ferumoxytol. The volume (100-400 µL) and rate (50-100 µL/sec) of contrast injection were equivalent for each agent.

Figure 1



Results Six of the 12 rats studies showed substantial susceptibility enhancement following microbubble injection similar to the success of previous studies (2). The microbubbles were observed to clearly distribute throughout the brain vasculature as shown in the pre- and post-contrast steady-state GE images in Figure 1. For this particular imaging session we were able to capture a high-resolution dataset when the signal enhancement for the bubbles was at a maximum. Unlike the rapid passage of ferumoxytol through cerebral tissue (duration < 10 sec, time-to-peak (TTP) ~ 5 sec) the duration of the microbubble signal enhancement (after jugular injection) was greatly prolonged (duration ~ 45-60 sec, TTP ~ 30 sec) (Figure 2). We found mixed results when using carotid artery injections. One rat showed bolus transit kinetics similar to ferumoxytol while 2 others demonstrated a variety of rapid and greatly prolonged transit times. The prolonged transit times prevented the calculation of RBC flow using standard first pass tracer kinetic methods.

Figure 2



Discussion: These preliminary studies have demonstrated the potential of using microbubbles as a susceptibility contrast agent in cerebral tissue. On average, the maximum measured $\Delta R2^*$ following microbubble injection was 1/3 of that produced by 3 mg/kg of ferumoxytol. The prolonged bubble transit times were unexpected given that RBC flow is equivalent to plasma flow in most vessels and slightly less than plasma flow in the microcirculation due to the Fahraeus effect. One possibility is that the lipid shell of the bubble interacts with the vessel endothelial wall resulting in a temporary attachment. Another mechanism could be the aggregation of bubbles in the injected bolus solution that lodge in the microcirculation and slowly separate over time by shear stress and plasma dissolution. The bubbles are less likely to aggregate in proteinaceous solutions so we are currently investigating the use of injectable mixtures of bubbles and blood plasma. In future studies we plan to evaluate the potential of RBC flow and volume measurements to assess brain tumor angiogenesis during growth and treatment response.

References: 1. Dharmakumar, R., *et al*., Magn Res Med 2002; 47: 264-273. 2. Wong, KK, *et al*., Magn Res Med 2004; 52: 445-452. 3. Lindner JR. *et al*., J Am Soc Echocardiogr 2002; May 15(5): 396-403.