

Assessment of Tissue Hypoxia and Vascular Reserve in a Porcine HindLimb Ischemia Model Using BOLD-MRI

Smita Sampath¹, Mitchel Stacy², Mark W Maxfield², Prasanta Pal³, Donald P Dione², and Albert J Sinusas²

¹Diagnostic Radiology, Yale University, New Haven, CT, United States, ²Cardiology, Yale University, ³Diagnostic Radiology, Yale University

Introduction: Atherosclerosis of the peripheral vessels, or peripheral artery disease (PAD) is a degenerative condition that can result in limb ischemia and is associated with limited mobility, morbidity and a high risk of death from heart attack or stroke. Non-invasive quantitative risk-stratification based on assessment of vascular function combined with patient-selective treatment planning and evaluation will improve outcome in these patients. The objective of our study is to provide insight on 1) the extent and distribution of hypoxia, and 2) the functional vascular reserve in response to distal cuff occlusion and vasodilatory agent nitroglycerine in a porcine animal model of hindlimb ischemia. This was achieved through the application of blood oxygen level dependent (BOLD) MRI techniques.

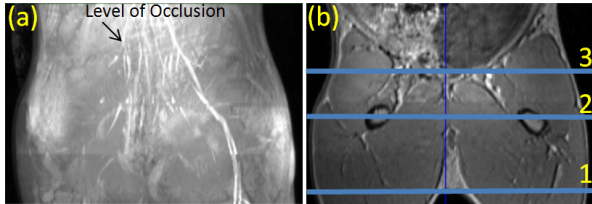


Fig. 1. (a) Maximum Intensity Projection (MIP) Image obtained from a 3D Time of Flight Acquisition shows missing vessel due to hindlimb occlusion model. (b) Position of representative slices described in following images are depicted on a cross-section of the MIP image. Note all slices are below the level of occlusion.

Methods: Experiments were conducted in the 3T MRI system (Trio TIM, Siemens Medical Systems) with maximum gradient strength of 40mT/m and maximum slew rates of 200mT/m/s. Imaging was performed acutely following femoral artery ligation of the right hindlimb in Yorkshire pigs. First, a Time of Flight (ToF) imaging sequence was used to confirm and establish location of hind limb occlusion (see Fig. 1). The imaging parameters used were: FOV: 260X210, imaging matrix: 320X260, flip angle: 60°, TR: 58, TE: 4.8, 48 slices/slab, slice thickness: 2mm, 3 overlapping slabs. Second, for hypoxia assessment, a T2* weighted single shot gradient echo BOLD pulse sequence with echo planar imaging readout was used with the following imaging parameters: field of view: 28X28 cm², pixel size: 2.2X2.2 mm², slice thickness: 5mm, echo time (TE): 20ms, 40ms, 60ms, 80ms, 100ms, repetition time (TR): 3000, and flip angle: 90 degrees. Multiple slices covering the volume of interest were acquired. T2* map was generated from acquired datasets for each slice (see Fig. 2a). Third, cuff occlusion experiment was performed by placing blood-pressure cuffs around the calves in both legs. Baseline imaging using the BOLD pulse sequence described above with identical imaging

parameters and a constant TE of 40ms was performed for 5 minutes, following which simultaneous inflation of both cuffs were conducted with continuous imaging for another 5 minutes. This was followed by simultaneous cuff deflation with continuous imaging for 5 minutes (see Fig. 2b). Finally, vasodilatory response was investigated under the influence of nitroglycerine.

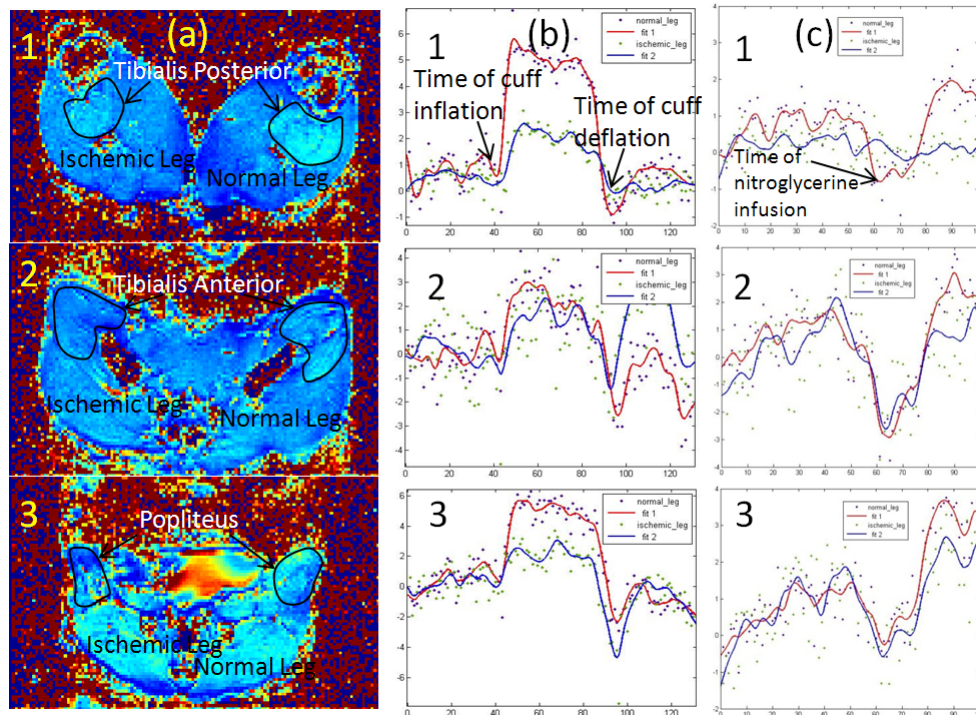


Fig. 2. (a) T2* maps for three representative slices depict hypoxia in ischemic leg in regions marked out corresponding to tibialis posterior, tibialis anterior and the popliteus muscles as compared to contralateral normal leg. BOLD normalized signal intensity changes in regions marked in (a) during (b) calf cuff occlusion experiment shows increased proximal compensatory response in normal leg compared to ischemic leg, and (c) nitroglycerine infusion experiment shows increased vasodilatory response in normal leg compared to ischemic leg. Red lines: normal leg, blue lines: ischemic leg.

vascular reserve during cuff occlusion or pharmacological vasodilation.

Conclusion: BOLD MRI is sensitive to assess regional distribution of hypoxia in response to hindlimb occlusion and is sensitive in the assessment of regional vascular reserve through the indirect assessment of tissue oxygenation during cuff occlusion and pharmacological vasodilation.

Again, the identical BOLD pulse sequence with TE of 40ms was used. Baseline imaging for five minutes was followed by continuous imaging following administration of nitroglycerine for 7 minutes (see Fig. 2c).

Results: Three representative slices from one animal below the level of occlusion (see Fig. 1) were selected for further investigation. T2* maps were created for these slices. Specific muscle groups, as highlighted in Fig. 2a exhibit differential T2* signal intensity between legs. Note hypoxia (decreased T2*) in highlighted muscle groups in the ischemic leg in comparison to normal leg. These differences in T2* were not observed in larger muscle groups such as the gastrocnemius or soleus muscles indicating potential collateral vessel supply to these muscle groups. Fig. 2b shows normalized BOLD signal intensity curves from cuff occlusion experiment. Compensatory vascular response due to distal cuff occlusion seems more pronounced in the normal leg as compared to the ischemic leg, especially for slices 1 and 3. Similarly, increased vasodilatory response is observed from the BOLD signal intensity curves in the normal leg versus ischemic leg following nitroglycerine infusion. These results indicate that inherent vasodilation that occurs in response to occlusion in the ischemic leg results in lower available functional