Simultaneous quantification of perfusion, venous oxygen saturation, and skeletal muscle T_2* in response to cuff-induced ischemia in the leg

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Introduction. Recent studies suggest that functional deficits present in patients with peripheral artery disease (PAD) may be detected by MRI measurement of parameters of vascular physiology in the lower extremity [1-4]. Through reactive hyperemia studies, it has been shown that PAD patients exhibit alterations in dynamics of perfusion [1]; venous oxygen saturation (SvO_2), a measure of vascular reactivity [2]; and skeletal muscle T_2*, a marker of tissue oxygenation [3,4]. While parallel measures of the post occlusive time-course SvO_2 and perfusion [5], or perfusion and T_2* [6] have been previously performed, a method for simultaneous quantification of perfusion, SvO_2, and T_2* has yet to be established. Concurrent acquisition of these parameters would offer a comprehensive functional assessment of the peripheral vasculature. The purpose of this study was to develop a MRI pulse sequence capable of simultaneously quantifying perfusion, SvO_2, and T_2*, to assess the sequence in healthy subjects, and to explore its results in PAD patients.

Methods. ***Theory.*** Simultaneous measurement of perfusion, SvO_2, and T_2* was achieved using an interleaved pulsed arterial spin labeling (PASL) and multi-echo GRE (Ox-BOLD) sequence, termed PASL/Ox-BOLD (Fig 1). For PASL, control and tag conditions were achieved using non-selective (NS) and slice-selective (SS) adiabatic inversion pulses, respectively. Image acquisition followed a 952 ms post-label delay (PLD) and perfusion was quantified as described in [7]. During the PLD, a keyhole Ox-BOLD sequence acquired data 3 cm distal to the PASL slice. This location was chosen to ensure perfusion is not affected by the Ox-BOLD interleave. Ox-BOLD high frequency k-space data was filled from a reference scan. As described previously [8], the difference in phase accumulation between blood and surrounding tissue from TE1 to TE2 was used to calculate SvO_2. Magnitude signal from TE1-TE5 was fitted to a mono-exponential function to calculate T_2*. Because the NS inversion affects both the PASL and Ox-BOLD slices, only Ox-BOLD images acquired after SS inversion were used, though the interleave was run every PLD to control for MT effects.

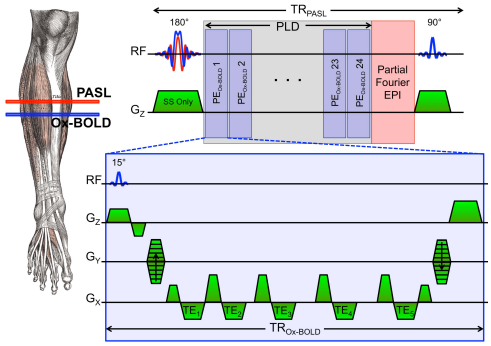

Fig 1. PASL/Ox-BOLD pulse sequence diagram with relative slice positions indicated on the left.

Experimental Protocol. In order to assess the impact of the PASL interleave on SvO_2 and T_2* quantification, and the effect of the Ox-BOLD interleave on the measurement of perfusion; results from the PASL/Ox-BOLD sequence were compared to those from a standard PASL and Ox-BOLD sequence run separately. In five young healthy subjects four consecutive acquisitions with PASL/Ox-BOLD (repeated twice), PASL, and Ox-BOLD alone were obtained; each with 1 min baseline, 3 mins occlusion, 6 mins recovery, and 1 min rest between scans. The protocol was repeated on a separate day. In three PAD patients (age = 71±2 years, ankle brachial index = 0.61±0.18) data was acquired with PASL/Ox-BOLD during 2 min baseline, 5 min occlusion, and 6 min recovery. For both healthy subjects and patients, reactive hyperemia was induced with a cuff (Hokanson) secured around the superior thigh, inflated to >200 mmHg. An 8-ch Tx/Rx knee coil (Invivo Inc.) was used for image acquisition at 3T (Siemens) with the following parameters: **PASL:** partial Fourier GRE-EPI with TR/TE=1000/9 ms, FOV=25×25 cm, ST=1 cm, matrix=80×50 (recon to 80×80), BW=1562.5 Hz/pixel; **Multi-echo GRE:** TR/TE1/TE2/TE3/TE4/TE5= 38.12/3.78/6.99/12.32/19.32/26.32 ms, FOV=96×96 mm, ST=1 cm, matrix= 96×24 (keyhole, recon with ref scan to 96×96), BW= 694 Hz/pixel. Perfusion was calculated in a ROI in the gastrocnemius, and time to peak (TTP) and peak hyperemic flow (PHF) were determined. SvO_2 was quantified in the larger peroneal vein, and washout time (t_s), time to minimum SvO_2, and overshoot (OS), SvO_{2max}-SvO_2 at baseline, [9] were calculated. A ROI was drawn in the soleus muscle, T_2* was calculated, normalized to the average baseline value, and relative T_2*$_{min}$, relative T_2*$_{max}$, and time to T_2*$_{max}$ (t_{max}) were determined. A paired Student's t-test was used to test for differences in measured values in the healthy subjects.

Table 1. Mean (SD) of time course parameters. [1] represents a statistically significant difference between methods.

	Young Healthy Subjects			PAD
	PASL	PASL/Ox-BOLD	Ox-BOLD	PASL/Ox-BOLD
PHF (mL/min/ 100g)	34.5 (5.0)	35.0 (3.9)		30.7 (4.3)
TTP (s)	20.9 (7.7)	19.2 (5.8)		100.7(38.3)
t_s (s)		11.7 (3.0)	10.7 (1.6)	34.0 (15.1)
OS (%HbO_2)		17.4 (6.0)	16.1 (5.2)	25.9 (8.1)
Relative T_2*$_{min}$		0.93 (0.03)	0.93 (0.02)	0.95 (0.01)
Relative T_2*$_{max}$		1.13 (0.05)[1]	1.17 (0.05)[1]	1.11 (0.03)
t_{max} (s)		30.1 (5.6)	29.8 (8.2)	97.3 (47.4)

Results. Fig 2 (a) compares average perfusion measured using PASL and PASL/Ox-BOLD; **(b)** shows SvO_2, and **(c)** shows relative T_2* measurements made with Ox-BOLD and PASL/Ox-BOLD. In all cases, error bars indicate SD. These average time courses illustrate the similarities of PASL/Ox-BOLD to PASL or Ox-BOLD, even across subjects. **Table 1** lists mean (SD) of the quantified time course parameters in both the healthy subjects using all pulse sequences, and in PAD patients using PASL/Ox-BOLD. In healthy subjects, no significant differences in perfusion or SvO_2 parameters were detected ($p>0.05$). The only significant difference was in relative T_2*$_{max}$, where Ox-BOLD was always higher than PASL/Ox-BOLD ($p<0.01$). Qualitatively comparing PAD patient data to healthy subjects' results, TTP, t_s, and t_{max} are delayed, PHF and T_2*$_{max}$ are decreased, and OS is increased.

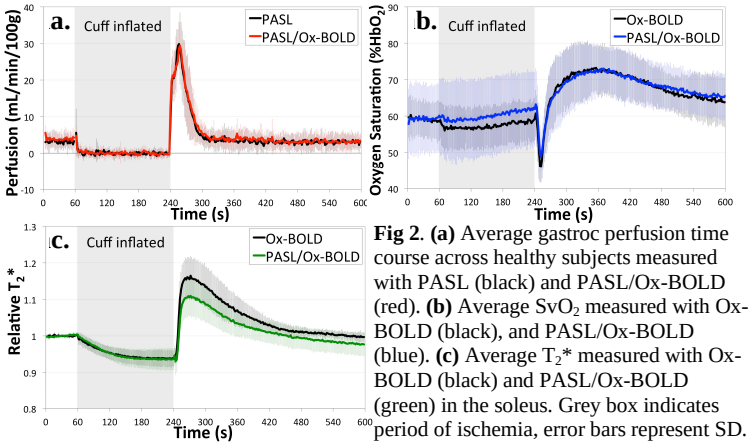

Fig 2. **(a)** Average gastroc perfusion time course across healthy subjects measured with PASL (black) and PASL/Ox-BOLD (red). **(b)** Average SvO_2 measured with Ox-BOLD (black), and PASL/Ox-BOLD (blue). **(c)** Average T_2* measured with Ox-BOLD (black) and PASL/Ox-BOLD (green) in the soleus. Grey box indicates period of ischemia, error bars represent SD.

Discussion. In healthy subjects, perfusion values for PHF and TTP agree with literature reported values [7]. The oximetry data, t_s and OS match with measurements made in young healthy subjects in the femoral vein [9]. T_2* data are also in agreement with previous studies [3], and although T_2*$_{max}$ differs between PASL/Ox-BOLD and Ox-BOLD, t_{max} is preserved. The reason for the difference in T_2*$_{max}$ requires further investigation. This work suggests that the simultaneous quantification of perfusion, SvO_2, and T_2* is possible with PASL/Ox-BOLD. In PAD patients a blunted and delayed hyperemic response is expected [1,3,9], and this is seen in all parameters with the exception of OS in SvO_2. These data represent a small cohort of patients with varied disease severity, yet even still a marked difference can be seen. Recruitment of additional PAD patients is ongoing. **Conclusion.** PASL/Ox-BOLD is capable of simultaneously quantifying perfusion, SvO_2, and skeletal muscle T_2* and can be used to capture the dynamic changes that occur in the lower extremity during reactive hyperemia.

References. [1] Wu et al, JACC 2009; [2] Langham et al, ISMRM 2011; [3] Ledermann et al, Circ 2006; [4] Potthast et al, Gefäße 2009; [5] Englund et al, ISMRM 2012; [6] Walvick et al, ISMRM 2012; [7] Raynaud et al, MRM 2001; [8] Fernandez-Seara et al, MRM 2006; [9] Langham et al, JACC 2010. ***Acknowledgements.*** NIH Grants R01HL075649 and 5T32EB 009384.