Multi-parametric assessment of vascular reactivity in peripheral artery disease

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Introduction: Peripheral artery disease (PAD), a manifestation of atherosclerosis in vessels supplying the lower limbs, causes significant morbidity and mortality [1]. The traditional marker of disease severity is the ankle-brachial index (ABI), which is the ratio of systolic blood pressure measured at the ankle and brachial artery. A reduction in ABI signifies the presence of stenoses in the macrovasculature, and even though this defines the diagnosis of PAD, the ABI does not specify spatial location of disease, is not sensitive to microvascular impairment, and cannot detect improvements due to pharmacologic or exercise therapy [2,3].

Recent studies suggest that functional deficits present in patients with PAD may be detected by dynamic imaging of the lower extremity using MRI [4-7]. Similar to cardiac stress testing, the peripheral vascular reactivity can be interrogated by measuring the rate of recovery following induced ischemia. Studies evaluating response to reactive hyperemia show PAD patients exhibit a blunted and delayed reperfusion [4], and a reduction in the rate of recovery of tissue oxygenation as evidenced by dynamic measurement of venous oxygen saturation (SvO_2) [5], and skeletal muscle T_2*, which is a marker of tissue oxygenation [6,7].

Perfusion, Intravascular Venous Oxygen saturation, and T_2* (PIVOT), a recently developed technique [8], allows for simultaneous, temporally resolved measurement of perfusion, SvO_2, and T_2* by interleaving a multi-echo GRE into the post-labeling delay of a pulsed arterial spin labeling (PASL) sequence. From the multi-echo GRE data, SvO_2 and T_2* are quantified; the difference in phase accrual between the vein and tissue in the first two echoes are used to calculate SvO_2 [9], and the amplitude from echoes 2-5 are fitted to a mono-exponential function to calculate T_2*. For PASL data, the normalized difference between images acquired following slice-selective or non-selective inversion is used to quantify perfusion [10]. Each parameter is quantified at 2-second temporal resolution. This multi-parameter approach may enhance the power for detection of disease or response to therapeutic intervention. The purpose of this study was to determine whether a relationship exists between ABI and dynamic indices of vascular reactivity measured with PIVOT.

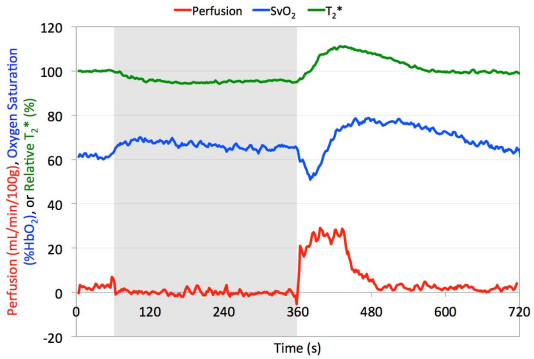

Figure 1. Perfusion, SvO_2, and T_2* reactive hyperemia time-course from a representative subject. Grey box indicates the period of arterial occlusion. During occlusion, T_2* decreases as oxygen is depleted from the capillary bed. Following cuff release, reactive hyperemia ensues, with an increase in perfusion and T_2*. The dip in SvO_2 after cuff release corresponds to the washout of deoxygenated blood from the capillary bed into the peroneal vein, and is followed by resaturation of venous blood as the oxygen saturation in the muscle

Methods: 48 patients (30 male, 69±8 years old) with PAD underwent ABI measurement, a treadmill-walking test using the Gardner protocol [11], and MRI. The Gardner protocol requires the patient to walk on a treadmill at 2 mph, initially with zero incline for two minutes, followed by an incline increase of 2 grades every 2 minutes thereafter. Patients indicated when they initially felt pain (claudication onset time, COT), and when they felt they could no longer walk due to the severity of pain (peak walking time, PWT). The MRI protocol consisted of dynamic imaging using PIVOT continuously throughout one minute of baseline, five minutes of proximal arterial occlusion, and six minutes of post-ischemic recovery. Data were acquired with an 8-ch Tx/Rx knee coil at 3T. Ischemia was induced via proximal arterial occlusion by inflating a cuff around the thigh to 75 mmHg above the systolic blood pressure. Perfusion was quantified in a region of interest in the soleus muscle, and peak hyperemic flow (PHF) and time to peak perfusion (TTP) were recorded. SvO_2 was measured in the larger peroneal vein, and washout time (time to minimum SvO_2) was recorded. T_2* was quantified in the soleus, normalized to the average baseline value, and the relative T_2*_{min}, T_2*_{max} and time to peak T_2* (TTP_{T2*}) were recorded.

Results: Figure 1 shows the perfusion, SvO_2, and T_2* time courses measured with PIVOT from a representative subject. Patients were grouped into severe (ABI<0.5), moderate (ABI between 0.5 and 0.7), and mild (ABI between 0.7 and 0.9) disease. **Table 1** lists the mean (standard deviation) of quantified time course parameters from PIVOT or from the treadmill-walking test. No correlation was seen between ABI and indices of functional disease impairment measured by treadmill-walking test, however significant correlations were found between ABI and both perfusion TTP and TTP_{T2*} (**Figure 2 a-c**). Additionally a Student's t-test showed significant differences between mild and moderate, mild and severe, and moderate and severe PAD for TTP and TTP_{T2*}. No correlation was found between ABI and the magnitude of PIVOT changes (PHF, T_2*_{min}, or T_2*_{max}) nor was a correlation seen between COT or PWT and any of the time-course derived metrics from PIVOT data.

Table 1. Mean (standard deviation) time-course parameters in severe (n = 7), moderate (n = 27), and mild (n = 14) PAD. p<0.05 for a Student's t-test comparing moderate to severe (#), mild to severe (*), and mild to moderate (+).

	ABI	COT (min)	PWT (min)	PHF (mL/min/100g)	TTP (s)	Washout time (s)	Relative T_2*_{min} (%)	Relative T_2*_{max} (%)	TTP_{T2*} (s)
Severe	0.42 (0.05)	4.6 (3.2)	7.8 (3.0)	33.3 (13.3)	113 (34)	46 (30)	90.4 (6.6)	105.4 (2.8)	119 (46)
Moderate	0.59 (0.05)	3.2 (1.9)	6.2 (3.1)	29.9 (13.9)	64 (29)#	34 (19)	92.1 (7.9)	105.2 (2.7)	82 (46)#
Mild	0.79 (0.07)	2.5 (1.7)	7.8 (5.9)	29.6 (14.2)	42 (15)*+	23 (11)*	95.7 (2.5)*	106.2 (3.4)	56 (14)*+

Discussion: Overall, a blunted and delayed hyperemic response is observed compared to a previous study using the same technique in young healthy subjects [8]. While COT and PWT represent the most physiologically relevant parameters for patients with PAD, they are subjective markers that depend upon pain tolerance. Thus, the lack of association between ABI or PIVOT-derived parameters and the treadmill walking times is not unexpected. The inverse correlation between ABI and perfusion TTP has been observed in a previous study using continuous ASL (CASL) [4]. With CASL, temporal resolution of perfusion was limited to 16 s, however using PIVOT, each parameter is sampled every 2 seconds. Since TTP in healthy subjects can be under 20 s [8], this improvement in temporal resolution is highly necessary. Wu, et al. also reported a progressive decline in PHF in patients with severe disease [4]. A correlation between ABI and the magnitude of response in any of the PIVOT-derived parameters has not been observed in this population, though a significant difference in T_2*_{min} was detected between mild and severe disease. Recruitment is ongoing, and the added value of monitoring the dynamics of perfusion, SvO_2, and T_2* recovery concurrently will be assessed through statistical models.

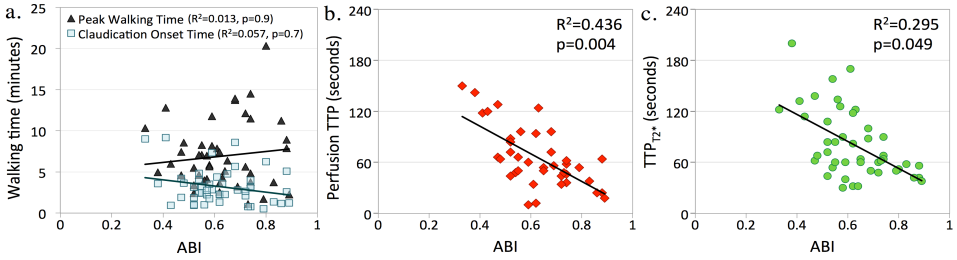

Figure 2. Correlation plots between ABI and COT and PWV (a), ABI and perfusion TTP (b), and ABI and TTP_{T2*} (c).

Conclusion: The function of the peripheral microvasculature can be interrogated in PAD patients by dynamic measurement of perfusion, SvO_2, and T_2* using PIVOT.

References: [1] Hirsch, et al. JAMA 2001; [2] Mohler, et al. Vasc Med 2001; [3] Murphy, et al. Circ 2012; [4] Wu, et al. JACC 2009; [5] Langham et al, JCMR 2013; [6] Ledermann et al, Circ 2006; [7] Potthast et al, Gefäße 2009; [8] Englund et al, JCMR 2013; [9] Fernandez-Seara, et al, MRM 2006; [10] Raynaud et al, MRM 2001; [11] Gardner, et al. Med Sci Sports Exerc 1991. ***Acknowledgements:*** Supported by an award from the American Heart Association and NIH Grants R01 HL075649 and HL109545.