Simultaneous measurement of microvascular and macrovascular blood flow and oxygenation in the leg

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Introduction. Peripheral vascular reactivity and dynamics of muscle metabolism may be better understood by measuring the temporal relationship of blood flow and oxygen saturation in micro and macrovasculature. Indeed, through reactive hyperemia studies, it has been shown that patients with peripheral artery disease (PAD) exhibit alterations in recovery dynamics of perfusion [1]; arterial blood flow [2]; venous oxygen saturation (SvO_2) [2]; and skeletal muscle T_2*, which is a marker of tissue oxygenation [3,4]. Previously, an interleaved pulsed arterial spin labeling (PASL) and multi-echo gradient recalled echo (GRE) sequence, termed Perfusion, Intravascular Venous Oxygen saturation and T_2* (PIVOT) was introduced, which allowed for the simultaneous acquisition of perfusion, SvO_2, and T_2* [5], however no single technique is currently capable of also measuring arterial blood flow. Concurrent acquisition of perfusion, SvO_2, T_2*, and arterial blood flow would offer a comprehensive functional assessment of the peripheral vasculature. Thus, the purpose of this project was to develop a technique capable of dynamically measuring several parameters of peripheral vascular reactivity.

Theory. Simultaneous measurement of perfusion, arterial blood flow, SvO_2, and T_2*, was achieved by interleaving a velocity-encoded keyhole multi-echo GRE sequence into the post-labeling delay (PLD) dead time of a PASL sequence (termed velocity-encoded PIVOT (VE-PIVOT)) (**Figure 1**). Similar to PIVOT, the multi-echo GRE acquires data at a slice 3 cm distal to the PASL slice to ensure that the perfusion measurement is not disturbed, and a slice selective saturation pulse follows the EPI readout to reset the magnetization each TR. As described previously [5], PASL data were used to calculate perfusion [6], SvO_2 was quantified by measuring the difference in phase accrual between blood and surrounding tissue from echoes 1 and 2 [7], and T_2* was measured by fitting the magnitude signal of echoes 2-5 to a mono-exponential function. The phase difference between echo 1 acquired with positive and negative gradient first moment was used to calculate velocity.

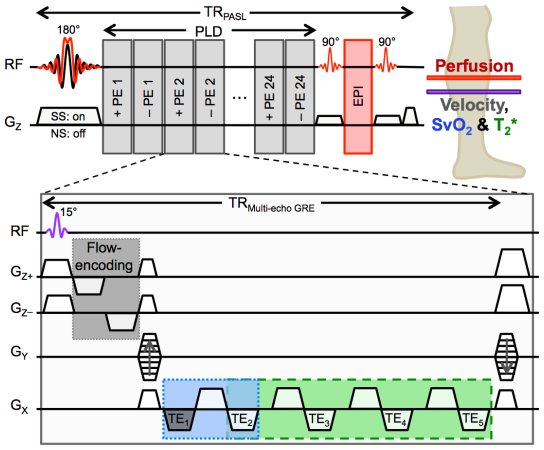

Figure 1. Velocity-encoded PIVOT pulse sequence. Echoes used to quantify SvO_2 (blue), T_2* (green), and velocity (dark grey) are shown.

Methods. ***Sequence Parameters.*** *PASL*: Slice-selective or non-selective adiabatic inversion with PLD=1.442 s followed by partial Fourier GRE-EPI with acquired matrix=80×50 (reconstructed to 80×80), FOV= 25×25 cm, slice thickness=1 cm, slice location = isocenter, TR/TE=1500/9 ms. *Velocity-encoded multi-echo GRE:* acquired matrix=96×24 (keyhole, reconstructed to 96×96 with fully-phase encoded reference image for SvO_2 and velocity analysis, acquired matrix = reconstructed matrix for T_2* analysis), FOV=96×96 mm, slice thickness=1 cm, slice location = 3 cm distal, TR/TE1/TE2/TE3/TE4/TE5= 28.31/5.25/8.93/14.61/19.76/24.91 ms, VENC = 40 cm/s.

Experimental Protocol. Reactive Hyperemia Evaluation: In order to assess the impact of velocity quantification on the measurement of perfusion, SvO_2, and T_2*, and vice versa, data acquired with VE-PIVOT were compared to PIVOT or to a phase contrast (PC-MRI) sequence in three young healthy subjects. Data were acquired throughout three ischemia reperfusion episodes, each with 1 min baseline, 3 mins occlusion, and 5 mins recovery. An 8-ch Tx/Rx knee coil was used for image acquisition at 3T. Perfusion was calculated in the soleus, and time to peak (TTP) and peak hyperemic flow (PHF) were determined. SvO_2 was quantified in the peroneal vein, and washout time (t_s = time to min SvO_2), and overshoot (OS= SvO_{2max}-SvO_2 at baseline), [9] were calculated. In an ROI in the soleus, T_2* was calculated, normalized to the average baseline value, and relative T_2*$_{min}$, relative T_2*$_{max}$, and time to T_2*$_{max}$ (TTP_{T2*}) were determined. Velocity and blood flow were quantified in the peroneal artery, and the maximum post-hyperemic velocity (v_{max}) and the time to peak (TTP_{Vel}) were recorded.

Exercise Protocol: To explore the potential of using VE-PIVOT to investigate dynamic changes of blood flow and oxygenation during exercise, one subject was continuously scanned throughout a series of five 30-second isometric plantar flexion contractions followed by 2 minutes of rest. T_2* and perfusion in the soleus, peroneal vein SvO_2, and peroneal artery blood flow were calculated. The response during the five contractions was then averaged to create a mean exercise time course.

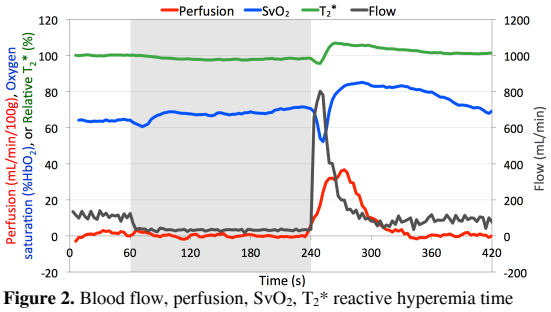

Figure 2. Blood flow, perfusion, SvO_2, T_2* reactive hyperemia time course. Grey box indicates period of proximal arterial occlusion.

Results. Table 1 lists the mean (SD) of quantified time course parameters acquired using VE-PIVOT, standard PIVOT, or PC-MRI. **Figure 2** shows the ischemia reperfusion time courses for blood flow, perfusion, SvO_2, and T_2* acquired with VE-PIVOT from a representative subject. **Figure 3** shows blood flow, perfusion, SvO_2, and T_2* time courses during the average of 5 exercise cycles.

Table 1. Average (standard deviation) time-course parameters measured with VE-PIVOT, PIVOT, or PC-MRI.

	PHF (mL/min/100g)	TTP (s)	V_{max} (cm/s)	TTP_{Vel} (s)	t_s (s)	OS (%HbO_2)	Relative T_2*$_{min}$ (%)	Relative T_2*$_{max}$ (%)	TTP_{T2*} (s)
VE-PIVOT	36.6 (8.6)	26 (6)	33.7 (7.0)	8 (2)	8 (2)	18.9 (6.5)	95.4 (0.7)	107.5 (0.5)	29 (6)
PIVOT	38.6 (4.5)	22 (7)			8 (4)	21.1 (2.8)	96.5 (0.8)	106.9 (1.0)	31 (8)
PC-MRI			37.4 (5.5)	11 (2)					

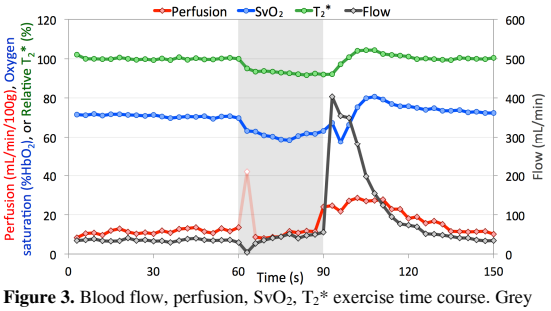

Figure 3. Blood flow, perfusion, SvO_2, T_2* exercise time course. Grey box indicates period of isometric contraction. Slight motion during the onset of contraction caused a spike in perfusion (white point).

Discussion. Results shown in Table 1 indicate that there is good agreement between PC-MRI and VE-PIVOT, implying that additional measurement of perfusion does not confound the phase contrast signal. Additionally, all quantified time-course metrics for perfusion, SvO_2, and T_2* measured with VE-PIVOT agree with PIVOT (no significant differences were detected) and are also in agreement with previous literature reported values [1-5]. Following cuff release, Figure 2 shows the expected hyperemic response in each of the measured parameters. Results in Figure 3 show that VE-PIVOT is sensitive to the changes in microvascular and macrovascular oxygen saturation and blood flow during and following isometric exercise. It is interesting to observe the relationship between arterial blood flow and perfusion. The post-contraction, or post-ischemic increase in peroneal artery blood flow, which greatly surpasses the magnitude of perfusion increase, may represent vascular shunting. This technique may be useful in development of biophysical models of blood flow and metabolism in skeletal muscle, and could provide dynamic information on vascular reactivity in patients with PAD. Recruitment of additional subjects is ongoing, and the application of this technique in PAD patients is planned for the near future. **Conclusion. Velocity-encoded PIVOT is capable of simultaneously measuring microvascular and macrovascular blood flow and oxygenation and can be used to capture the dynamic changes that occur in the lower extremity during reactive hyperemia and exercise.**

References. [1] Wu et al, JACC 2009; [2] Langham et al, JCMR 2013; [3] Ledermann et al, Circ 2006; [4] Potthast et al, Gefäße 2009; [5] Englund et al, JCMR 2013; [6] Raynaud et al, MRM 2001; [7] Fernandez-Seara, et al, MRM 2006; ***Acknowledgements.*** This work was supported by an award from the AHA and NIH Grants R01 HL075649 and R01 HL109545.