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Letter to Editor

A lower limb BOLD-MRI tissue perfusion protocol correlate to clinical disease stage, objective functional limitations, and health-related quality of life in patients with peripheral arterial occlusive disease

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While peripheral artery occlusive disease (PAOD) by large is a clinical diagnosis, further characterization of the ischemic state, procedural planning, and longitudinal follow-up after revascularisation are mainly based on imaging that delineates the arterial vasculature. Although several potential techniques have been suggested [1], there is still no clearly established imaging technique that directly quantifies the crucial PAOD pathophysiological process-tissue perfusion in the lower limb.

Blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI) is a noninvasive functional MRI technique that allows for the quantification of skeletal muscle perfusion without the use of contrast agents. The BOLD signal depends on differences in the magnetic properties of oxygenated and deoxygenated hemoglobin, and regional changes in the oxy/deoxyhemoglobin ratio can be recorded by T2* weighted MRI sequences.

We previously showed the feasibility of this technique in PAOD and found that a tissue reperfusion BOLD-MRI protocol reliably differentiated patients with PAOD from healthy controls without PAOD, with the most discriminative parameter being the time to peak of the T2* signal following the release of a thigh cuff after five minutes of provoked ischemia [2]. However, to be clinically useful, this BOLD-MRI technique ideally should be sensitive also to clinical disease stage and responsive to both differential functional limitations as experienced by PAOD patients and to clinical changes following improvements or deteriorations of the condition. The aim of this pre-specified secondary analysis was accordingly to explore the correlations between the most discriminative BOLD-MRI perfusion parameter (i.e. time to peak of the T2* signal following cuff release) and:

1. Anatomic disease stage according to the Trans-Atlantic

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Society Consensus (TASC II) classification system, estimated from gadolinium-contrast MR angiography images

2. Objective walking capacity as measured during a graded treadmill test

3. Health-related quality of life as measured with the PAOD-specific health-related quality of life instrument VascuQoL-6.

The design of this small feasibility study, as well as details regarding the PAOD BOLD-MRI imaging protocol have been reported previously [2]. In brief, twenty-two patients (mean age 73.5 ± SD 4.1 y; 12 male) with confirmed intermittent claudication of vascular origin and 10 healthy volunteers (mean age 67.9± SD 6.2 y; 8 male) without PAOD consented to participate, and the study was approved by the Regional Ethical Review Board in Gothenburg (entry no. 1157-17). All patients underwent the clinical exam, independently responded to the VascuQoL-6 questionnaire, and underwent a graded treadmill test. The BOLD-MRI examination was thereafter performed on a 3 Tesla whole-body MRI scanner (Magnetom Skyra, Siemens Healthineers, Erlangen, Germany) with a large 4-channel flex coil. MRI measurements were performed for 660 seconds using a 2D multi-echo gradient echo, and images were collected from the widest part of the calf. Ischemia and reperfusion during the diagnostic procedure were provoked by transient compression using an inflatable thigh cuff fixed at mid-thigh (ERKA, Berlin, Germany) and an automatic tourniquet insufflation device (Zimmer, ATS 750, USA). Rapid inflation was done one minute after the T2*-measurements started at an inflation pressure preset to 50 mmHg above the recorded systolic pressure of the right arm. After five minutes, the tourniquet pressure was rapidly released. The T2*-images were continuously acquired with a temporal resolution of 3.2 seconds at rest (1 min), during compression (5 min), and during the reperfusion phase (5 min).

For evaluation of perfusion effects in the gastrocnemius and soleus muscles, T2*-maps displaying the blood oxygenation level were created. The key parameter of interest was the time to T2* max value after cuff deflation (time to peak, TTP), and the correlations between the TTP parameter and 1) treadmill maximal walking distance, 2) VascuQoL-6 scores, 3) pre-recorded Rutherford class, 4) ankle-brachial index and 5) TASC class were assessed with Spearman rank correlation. Correlation coefficients (r_s) at 0-0.39 was arbitrarily considered weak, 0.40-0.59 as moderate, and 0.6-0.1 as strong.

All MRI examinations were successfully performed and the cuff compression period was well tolerated by all patients. Moderate to strong correlations were observed between the gastrocnemius and soleus TTP values and the maximal treadmill walking distance, disease-specific HRQoL, and Rutherford class (Table 1).

In conclusion, the BOLD-MRI TTP parameter correlated moderately to strongly with a variety of clinically relevant parameters that reflect PAOD severity. The results of this feasibility study, therefore, lend support that functional MRI techniques may add value to the overall diagnosis and management of PAOD patients. Further studies will focus on whether BOLD-MRI is also responsive to resultant tissue perfusion changes following lower limb revascularization, and whether the technique may add value in the management of patients with more severe ischemia i.e., in patients with chronic limb-threatening ischemia.

Table 1: Correlation matrix displaying observed correlations between the BOLD-MRI time to peak parameter (TPP), maximal treadmill walking distance, VascuQoL-6 sum scores, and Rutherford class.

	TPP in the gastrocnemius muscle	TTP in the soleus muscle
Treadmill maximal walking distance (n=22)	r_s =-0.47*	r_s =-0.50*
VascuQoL-6 sum score (n=32)	r_s =-0.55**	r_s =-0.58**
Rutherford class (n=32)	r_s =0.57**	r_s =0.64**
Ankle-brachial index (n=32)	r_s =-0.78**	r_s =-0.75**
TASC II class (n=21)	$r_{s=}$0.27 (n.s.)	$r_{s=}$0.34 (n.s.)

**=significant at the .05 level, **=significant at the .01 level (two-sided tests) n.s.=not significant*

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