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EDITORIAL COMMENT

Being BOLD in Critical Limb Ischemia*

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"Begin, be bold, and venture to be wise."
– Horace (1)

The management of peripheral arterial disease (PAD) still heavily relies on clinical judgment and the use of the ankle-brachial pressure index (ABPI), originally described in 1950 for the noninvasive diagnosis of lower extremity arterial disease (2). With the exception of technical improvements in the angiographic detection of macrovascular disease using magnetic resonance (MRI) and computed tomographic imaging, we are not "wiser" with regard to obtaining a metric of tissue level perfusion. Tissue oxygenation is, after all, the ultimate gold standard that may allow better discrimination of what the end organ is experiencing and facilitate clinical decision making.

Although multiple modalities have been proclaimed as able to provide such information, clinically embracing such modalities has been challenged by poor precision, poor reproducibility, and superficial resolution (3). The use of MRI methodologies to determine tissue level oxygenation information is not new, but rather dates back to the early 1990s when Ogawa et al. (4) first utilized blood oxygenation level–dependent (BOLD) contrast as a "functional" mapping technique to determine improvement in blood flow and oxygenation to mental processes. The BOLD technique measures inhomogeneities in the magnetic field due to changes in the level of oxygen. Oxygenated blood is diamagnetic whereas deoxygenated blood is paramagnetic. Thus, a high ratio of deoxygenated/oxygenated blood results in microscopic field inhomogeneity and a subsequent loss in intravoxel phase coherence. Although BOLD was performed in 1998 to study tissue oxygenation in the lower extremities, the first use of BOLD in PAD was not reported until 2006 (5,6).

While appealing as a clinically relevant index, the use of BOLD in PAD has remained in the research domain for multiple reasons. Of foremost importance is that the lower extremity poses challenges in terms of generating adequate BOLD signal. Although total perfusion at rest to the skeletal muscle in healthy adults is large, accounting for up to 17% of the cardiac output (900 ml/min), the perfusion rate averaged over the entire organ is a mere 3 ml/100 g/min. This contrasts with the brain and the liver, which receive 56 ml/100 g/min and 100 ml/100 g/min, respectively (7). Augmentation of flow in response to a provocative stimulus is often leveraged as a tool to exaggerate perfusion (8). The increase in perfusion with exercise or pharmacological vasodilation is dramatic in the skeletal muscle, with a 20-fold to 40-fold increase in flow. Still, the relative increase in signal intensity seen with BOLD in the extremity is modest at best (8).

In critical limb ischemia (CLI) there are multiple additional challenges for BOLD imaging. First, there is limitation not only in resting flow but also in recruitable flow due to a maximally dilated, anatomically restricted arterial bed owing to extensive multilevel, multisegment disease. This precludes delivery of an adequate "pressure head" of hemoglobin to generate signal. Further, long contact time between the blood, myoglobin, and oxygen-consuming myocytes occurs, resulting in efficient deoxygenation of oxyhemoglobin and a higher final concentration of deoxyhemoglobin, contributing to an overall reduction in peak signal and the method's dynamic range. Second, the multiple parameters require laborious manual analysis, which may be clinically impractical. Third, prior studies have suggested that measures such as time-to-peak and T2* maximum may not be easily identifiable or reproducible with a coefficient of variation of up to 51% (9).

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Finally, related to all of the above factors, discrimination of 1 PAD patient from the other, or assessment of small changes, may not always be possible.

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The work by Bajwa et al. (10) in this issue of the *Journal* represents an improvement over prior BOLD approaches and ventures to be "wiser" in approaching tissue oxygenation in CLI. The authors should be congratulated for incorporating technical improvements including use of 3-T, higher spatial resolution (allowing for accurate region-of-interest placement, avoiding blood vessels that may contaminate T2* values), and use of a larger number of echo times (14 vs. 3 to 4), allowing for accurate delineation of T2* decay. Traditional parameters such as time-to-peak (with reactive hyperemia), time-to-half ischemia, and maximum T2* were examined in addition to other semi-automated measures, such as gradient of rise of T2* signal (Grad) and changes in T2* signal during ischemia (signal reduction during ischemia). Additional strengths include testing of reproducibility and validation with histological measures of capillary density (capillary/fiber ratio and CD31 staining).

The main findings were the demonstration of feasibility and reproducibility of BOLD. Importantly, the measures improved with revascularization given additional differential improvement in BOLD indexes (but not ABPI) between patients who differed in the patency status of the superficial femoral artery. Superficial femoral artery and profunda femoris patency are well-known determinants of limb salvage and outcomes in patients with CLI (11). BOLD measurements could still be obtained in patients in whom ABPI measurements were unobtainable (5 of 13 patients) owing to calcified arteries. The authors obtained muscle biopsy specimens and demonstrated reduced capillary fiber ratio in the ischemic area at the level of BOLD imaging. Capillary fiber ratio was reduced at the BOLD level compared to better-perfused proximal zones. (BOLD perfusion was not performed proximally).

This study's clinical relevance lies in the fact that an objective measure of perfusion may facilitate decision making. Although BOLD has been previously used in patients with intermittent claudication, the poor signal-to-noise ratio (SNR) and lack of dynamic range have been major limitations (6). The use of the technique in CLI and discriminate response following revascularization are major strengths of this paper. There were weaknesses, too, including the inability to discriminate between those with or without diabetes and smokers from nonsmokers and the fact that a subset of patients may not be able to be imaged (those who cannot lie still due to rest pain or those with extensive tissue damage or recent surgery).

How does this method compare to other MRI approaches such as dynamic contrast enhancement and arterial spin labeling (ASL) that provide information on tissue-level perfusion? The compelling advantage of dynamic contrast enhancement is superior SNR, owing to the use of gadolinium-based contrast agents. However, gadolinium administration may be an issue in patients with CLI, many of whom have chronic kidney disease. Moreover, for absolute quantification of perfusion, knowledge of the concentration of contrast in the blood plasma is required but may be difficult to obtain in CLI patients who often lack discernible vessels below the knee. ASL uses magnetically "labeled" arterial blood as an endogenous tracer and measures the delivery of the labeled blood into tissue, allowing for perfusion quantification in absolute units (12). As in BOLD, low SNR is the main drawback of ASL and may render the evaluation of CLI patients difficult, although promising results have been obtained in patients with intermittent claudication (13).

Ultimately, the availability of noninvasive approaches that provide insights into tissue perfusion and response to therapeutic intervention may reinvigorate interest in new therapeutic modalities. However, we may first need to be bold in CLI, by exploring new approaches that may ultimately lead to wisdom.

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