**EDITORIAL COMMENT**

**BOLD New Directions in Myocardial Ischemia Imaging—Myocardial Oxygenation Assessment by Cardiac Magnetic Resonance*\(^\text{1}\)**

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Myocardial ischemia results from an imbalance between oxygen supply and demand. After coronary occlusion, oxygen supply and demand mismatch produces a series of physiological alterations that can precede clinical symptoms (1). Impaired myocardial perfusion is an early event in the “ischemic cascade” that can be assessed using clinically available noninvasive imaging. Both extent and severity of perfusion deficits have been shown to predict longitudinal clinical outcomes, including cardiovascular mortality risk (2). Accordingly, current American College of Cardiology/American Heart Association guidelines support of stress perfusion imaging for assessment of symptomatic patients with intermediate or high pre-test likelihood of coronary artery disease (CAD) (3).

Although important information can be gained from myocardial perfusion imaging, this approach evaluates only a single aspect of the ischemic cascade. Although perfusion assesses oxygen supply, it does not evaluate myocardial oxygen demand and, is therefore, an incomplete index of ischemic physiology. Animal studies using direct coronary blood sampling have demonstrated that oxygen consumption is reduced in the setting of myocardial hibernation (4), a condition in which contractile function is down-regulated in parallel with chronic hyperperfusion. The importance of myocardial oxygen consumption has also been demonstrated using positron emission tomography (PET) based \(^{11}\)C-acetate imaging. Among patients with obstructive CAD, preserved myocardial oxidative metabolism on PET has been shown to differentiate viable from nonviable myocardium, and this approach has performed favorably for prediction of functional response to revascularization compared with other PET methods such as assessment of glucose metabolism (5,6). Oxygen supply and demand can also be independent of one another. For example, in the context of acute myocardial infarction, delayed revascularization can restore coronary blood supply to transmurally infarcted myocardium in which cellular metabolism is minimal (7), potentially leading to a scenario in which perfusion is normal, but oxygen consumption is negligible. Taken together, these concepts illustrate that oxygen supply and demand can individually vary in response to physiological stimuli, resulting in differing magnitudes of myocardial ischemia that may not be fully discernable via assessment of perfusion alone.

Cardiac magnetic resonance (CMR) imaging holds the potential to assess both myocardial perfusion and oxygen consumption. Unlike PET, CMR does not entail exposure to ionizing radiation, and is thereby well suited to assess temporal changes in cardiac physiology. Perfusion can be assessed based on regional signal intensity differences during first-pass infusion of gadolinium-based contrast agents. CMR stress perfusion imaging is an established clinical technique that has been shown to yield favorable diagnostic performance for obstructive CAD compared with other modalities (8,9). Independent of perfusion, CMR can assess myocardial oxygenation consumption via a technique termed blood oxygen level–dependent (BOLD) imaging. This technique, which can be performed without contrast administration, is predicated on differences in magnetic susceptibility between oxyhemoglobin and deoxyhemoglobin. Whereas oxyhemoglobin is mildly diamagnetic, deoxyhemoglobin is paramagnetic, and this latter property produces local field gradients between red blood cells and their surroundings. The shift in frequency caused by these gradients affects transverse (T2) relaxation times, with red blood cell deoxygenation (deoxyhemoglobin) causing T2 to decrease. BOLD imaging exploits T2 differences between oxyhemoglobin and deoxyhemoglobin, and thus provides a measure of myocardial oxygen consumption. Like perfusion, BOLD imaging can be performed during rest and pharmacological stress conditions to assess dynamic changes in myocardial physiology. BOLD imaging has been validated in animal models and has been shown to be feasible in human studies (10–12). However, clinical application has been limited, possibly due to variable image quality yielded by conventional pulse sequences for BOLD assessment.

In this issue of the *Journal*, Arnold et al. (13) evaluate clinical application of BOLD imaging for detection of CAD. To optimize BOLD image quality, the investigators utilized high field strength (3-T) CMR and applied a

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recently developed approach, whereby data was acquired using a T2-prepared, steady-state free precession pulse sequence sampled across multiple RR intervals. Both BOLD and perfusion CMR imaging were performed at baseline and during adenosine stress, with results analyzed quantitatively. Diagnostic performance of BOLD imaging for obstructive CAD was compared with perfusion CMR among patients who underwent invasive angiography. Myocardial oxygen consumption, as manifest on BOLD, was also examined in relation to clinical indexes as well as conventional CMR findings (i.e., perfusion, hyperenhancement) to assess whether oxygen consumption varies in relation to physiological substrate. Regarding diagnostic performance, results demonstrated that BOLD yielded slightly lower accuracy (86%) than did perfusion CMR (91%), with differences between the 2 techniques attributable to lower specificity for BOLD (72%) compared with perfusion (89%). Additionally, whereas this study found that the likelihood of an abnormal BOLD response generally declined as perfusion-evidenced hyperemic blood flow increased, the 2 indexes correlated weakly ($r = 0.26$), as evidenced by the fact that half of hypoperfused segments demonstrated no evidence of deoxygenation.

Based on current results, is BOLD imaging ready for widespread clinical application to test for CAD? Further incorporation of physiological indexes is certainly attractive as a potential means of better characterizing ischemic burden. However, although findings from this comprehensive study are encouraging, several issues are worth considering. First, despite application of a sophisticated BOLD technique to a population at increased likelihood for CAD (i.e., all patients undergoing x-ray angiography had symptomatic chest pain clinically deemed to warrant further evaluation via invasive testing), BOLD yielded a 2-fold higher false positive rate (12%) than did perfusion imaging (5%). Although it is plausible that this may reflect subtle changes in myocardial oxygen consumption that occur in the absence of perfusion-evidenced deficits or angiography-evidenced coronary obstruction, an alternative possibility is that current generation BOLD techniques remain compromised by low signal intensity and/or image artifacts that mimic physiological abnormalities. Additionally, BOLD imaging as applied in this study was limited to a single short-axis slice. This approach is suboptimal for assessment of global ischemia and distal CAD, emphasizing the need for novel technical approaches that can improve BOLD spatial coverage without compromising signal-to-noise or overall image quality. Three-dimensional data acquisition with navigator-based respiratory motion compensation (to eliminate breath-holding) could potentially be used to improve BOLD spatial coverage (12).

More broadly, although the current study provides a valuable comparison of BOLD to state-of-the-art CMR perfusion, it is important to recognize that clinical stress CMR protocols typically integrate perfusion data with at least 2 additional components—systolic function and infarct assessment. A strategy of integrated stress CMR interpretation has previously been shown to improve test performance for CAD (14), and a similar interpretive approach has been used in multicenter studies (9). In the context of the previously noted false positive rates in this study, it is unlikely that current generation BOLD techniques are ready to replace perfusion as a first-line approach to identify obstructive CAD. Although the investigators also report novel findings concerning BOLD in the context of nonobstructive CAD, the clinical implications of such imaging findings are uncertain. Thus, an outstanding question concerns whether BOLD imaging incrementally improves diagnostic test performance or prognostic assessment above and beyond integrated perfusion/infarction FUNCTIONAL data to warrant its inclusion as an additional component of clinical stress CMR protocols.

A particularly compelling aspect of BOLD imaging concerns its potential to elucidate the influence of local and systemic conditions on myocardial energy utilization. Integration of BOLD with assessment of myocardial function, structure, and tissue characteristics offers the prospect of further expanding the multifaceted capabilities of CMR. The current study yields important insights into potential alterations in oxygen consumption that may occur in the context of myocyte cell necrosis. Although perfusion-evidenced hyperemic response was lower ($p < 0.0001$) in regions with hyperenhancement, oxygen consumption (as manifested by BOLD signal intensity change) did not differ ($p = 0.26$). This finding may be explained by several potential mechanisms. As posited by the investigators, regions of viable but hibernating myocardium may down-regulate oxygen demand in response to decreased perfusion, paralleling reductions in energy utilizing processes such as contractile function. Alternatively, in the setting of non-transmural infarction, residual viable myocardium may be sufficient to preserve "normal" cumulative oxygen demand as measured on a per segment basis. Although this study did not examine oxygen consumption in relation to infarct transmurality, it is reasonable to anticipate that oxygen consumption would differ between regions of subendocardial and transmural infarction. Beyond infarct transmurality, examination of serial changes in oxygen consumption and systolic contractility could be used to test the utility of BOLD for predicting functional response to therapeutic interventions such as coronary revascularization. Further study is warranted to explore these issues.

Magnetic resonance imaging is a relatively new technology—the first human body examination occurred in 1977 and took nearly 5 h to produce a single image (15). In the subsequent 35 years, MRI has experienced marked technical advances and is now well established as a critically important tool for cardiovascular assessment. Myocardial oxygenation imaging holds the potential to further improve ischemia evaluation and yield new physiologic information. The current study by Arnold et al. (13) provides important new insights concerning clinical performance of state-of-the-art BOLD imaging.
and raises intriguing questions concerning the manner in which oxygen consumption is altered in relation to changes in myocardial perfusion, structure, and function. Further advances in BOLD techniques are to be expected, which should enable broader application for assessment of myocardial physiology.

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