To BOLDly Go Where Positron Emission Tomography Has Been Before

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Atherosclerotic disease remains concealed for many years and becomes clinically overt only when the growth of atherosclerotic plaques and the adverse remodeling of the arterial wall reach a critical stage that results in impairment of blood flow, ischemia, and angina. Large epicardial arteries have a diameter ranging from a few millimeters to \( 500 \mu \text{m} \) and are visible at coronary angiography. Prearterioles (diameter from \( 500 \text{ to } 100 \mu \text{m} \)) and arterioles (diameter \( <100 \mu \text{m} \)) are beyond the resolution of current angiographic systems and hence are not visible at angiography. Each compartment is regulated by distinct mechanisms, and vascular resistance is distributed in series along the coronary vascular bed.\(^1\) The oxygen supply to the myocardium is determined by arterial oxygen saturation and myocardial extraction, which are relatively fixed in normal perfusion conditions. At constant distending pressure, variations of flow in epicardial coronary arteries can be achieved by means of intracoronary injection of arteriolar vasodilators.\(^2\) Near maximal hyperemia can be achieved using coronary vasodilators such as adenosine or dipyridamole, which induce vasodilatation, mainly in the coronary microcirculation. The functional severity of a stenosis cannot be estimated by anatomic imaging such as x-ray coronary angiography or multislice computed tomography, and, in addition, diffuse atherosclerosis and extensive arterial remodeling may contribute to the dissociation of anatomic and functional measurements of coronary stenosis severity. Therefore, the functional significance of coronary stenoses can only be evaluated by measures of coronary flow, and commonly the flow reserve, which is the ratio of nonregulated maximum (hyperemic) and autoregulated (resting) flow. This characterization requires accurate quantitative measurements of pressure and/or flow and can be estimated invasively as fractional flow reserve\(^3\) or measured noninvasively with positron emission tomography (PET).\(^3\)

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The relationship between resting and hyperemic myocardial blood flow and severity of coronary stenoses in patients with coronary disease has been studied using oxygen-15-labeled water (\( H_2^{15}O \)) and nitrogen-13-labeled ammonia (\( ^{13}\text{NH}_3 \)). PET is at present the only imaging modality capable of absolute measurement of regional myocardial perfusion and oxygen metabolism with \( ^{11}C \)-acetate. Acetate is a free fatty acid with a short chain length of 2, which enters the tricarboxylic acid cycle after conversion to Acetyl-CoA. Acetate labeled with \( ^{11}C \) is used to measure the flux of the tricarboxylic acid cycle and is tightly coupled to MVO₂. Depending on the work load, \( ^{11}C \)-acetate clearance can be monoexponential at rest or biexponential during exercise, pacing,\(^4\) or pharmacological stress with dobutamine.\(^5\) The accuracy of MVO₂ determination is dependent on concentration of glutamate, aspartate, and tricarboxylic acid cycle intermediates, which can vary among species and are affected by ischemia.\(^6\) Absolute measurements, though, come at a price, and the widespread clinical utilization of this approach for the evaluation of the functional significance of coronary stenoses has been limited by the fact that \( H_2^{15}O, ^{13}\text{NH}_3, \) and \( ^{11}C \)-acetate require a cyclotron on site for their production.

In the last decade, substantial technical development has been achieved in the assessment of myocardial perfusion by means of cardiovascular magnetic resonance (CMR), exploiting the first-pass kinetics of \( T_1 \)-enhancing extracellular gadolinium chelates.\(^8\)\(^9\) The gadolinium contrast agent diffuses into the myocardial interstitial space and the signal intensity increases are proportional to myocardial perfusion. There is another CMR approach, which is the blood oxygen level–dependent (BOLD) technique, and this does not require a contrast medium. This exploits the difference between oxygenated hemoglobin, which is slightly diamagnetic and deoxyg-derived hemoglobin, which is paramagnetic and causes a signal loss in \( T_2 \) or \( T_2^* \)-weighted images. The \( T_2^* \) approaches generally use a simple gradient echo sequence with a relatively long echo time to increase the sensitivity. Although the inherent sensitivity of these methods to oxygenation should be at least as high for \( T_2 \), the signal-to-noise ratio tends to be low and the images tend to be affected by image artifacts caused by magnetic field inhomogeneity, blood flow, and cardiac motion. The \( T_2 \) approaches have either used a turbo spin-echo with a relatively long echo time or a \( T_2 \) prepared bSSFP (steady-state free precession) sequence that takes advantage of the high signal-to-noise ratio and inherent quality of that sequence.\(^10\)

In this issue of *Circulation: Cardiovascular Imaging*, 2 articles validate advanced BOLD CMR techniques against PET for the assessment of regional myocardial oxygen extraction fraction in humans with or without coronary artery disease\(^11\) and in experimental animal models of coronary stenosis during metabolic (dobutamine) and endothelium-
independent vasodilation (adenosine),\textsuperscript{12} Karamitsos et al\textsuperscript{11} validated the clinical use of 3T CMR against PET with H\textsubscript{2}\textsuperscript{15}O and conventional angiography. They studied both normal volunteers and patients with coronary artery disease with various degrees of stenosis. In normal subjects, adenosine infusion induced a sizeable 17% increase of BOLD signal intensity; however, in regions subtended by a stenotic artery, this increase was suppressed to only 3.4%. Interestingly, in remote segments without evidence of anatomic stenosis, the BOLD signal intensity was intermediate (9.95%), highlighting the abnormality of the response to hyperemic stimuli of those myocardial regions that are subtended by an angiographically “normal” artery but where diffuse disease might limit maximal flow as demonstrated also by the PET measurements. BOLD showed moderate sensitivity to identify ischemic segments against PET, but 40% of myocardial segments with myocardial blood flow below the cutoff value of 2.45 mL/min/g established in this study did not show deoxygenation. To set a cutoff for all the patients irrespective of age might be misleading, a stenosis >75% with no impairment of the microcirculation may not be flow-limiting, and the anatomic stenosis severity fails to indicate the actual coronary flow capacity. Indeed, a coronary flow reserve of 2 can be found in normal individuals over the age of 60.\textsuperscript{13} The actual impact of performing this study at 3 T is not certain. In principle, the higher field would be expected to increase the signal-to-noise ratio and increase the sensitivity to different levels of oxygenation; however, increased shimming and other artifacts were shown to be a potential problem. BOLD interrogation of the ischemic myocardium was limited to a single midventricular slice, whereas the established nuclear techniques can explore the whole heart, and this coverage would have to be increased for any potential clinical applicability of BOLD. The comparative data when viewed on a per-segment basis appear to show some scatter, and, although this can be a result of physiological variability or inadequate alignment between PET and BOLD images, the possibility cannot be neglected that noisy BOLD measurements within a limited dynamic range are a contributing factor. The question therefore remains open as to whether we are any closer to a robust BOLD method using the higher magnetic field strength that could be used on an individual patient basis to make therapeutic decisions.

McComnis et al\textsuperscript{12} propose a combination of first-pass perfusion and BOLD methods to evaluate the regional changes in myocardial perfusion and oxygenation induced by an acute coronary artery stenosis at rest and during pharmacological hyperemia in anesthetized dogs. First-pass perfusion was performed using a macromolecular contrast agent that is almost exclusively intravascular, has rapid clearance, and has an R1 relaxivity that is 3-fold higher than extravascular gadolinium contrast agents at 1.5 T. In a rather complex protocol, some of the dogs were instrumented with external occluders to induce moderate (75%) or severe (95% to 100%) stenosis. The animals underwent both PET and CMR at rest and during either dipyridamole or dobutamine infusion to induce a wide range of myocardial perfusion and oxygenation changes. PET myocardial perfusion was measured with H\textsubscript{2}\textsuperscript{15}O and MVO\textsubscript{2} with \textsuperscript{13}C-acetate. The analysis was limited to 4 segments of a single short-axis slice. The agreement between PET and CMR perfusion data in the range 1 to 4 mL/min/g was reasonably good, although it would have been interesting to have also lower perfusion values that are to be expected with a 95% stenosis during dipyridamole infusion in species with a less developed collateral network.\textsuperscript{14} Similarly, there was a good agreement between CMR and PET for regional MVO\textsubscript{2}, whereas oxygen extraction fraction derived from BOLD T\textsubscript{2}-weighted images showed a moderate agreement and a systematic underestimation in comparison with PET.

In conclusion, the absolute measurement of myocardial perfusion with CMR is now a reality that has been validated by various groups,\textsuperscript{8,15,16} is reproducible, and is starting to be applied in human cohort studies.\textsuperscript{17} The next step to spread the application in everyday clinical practice is the standardization of protocols, pulse sequences, and straightforward applicable models for fully quantitative analysis. On the other hand, the evaluation of MVO\textsubscript{2} appears more elusive because of a number of methodological constraints. The 2 articles in this issue of Circulation: Cardiovascular Imaging provide further encouragement that CMR has the capability to measure myocardial blood flow and oxygenation on an individual basis. However, there is still considerable work required first to establish the best methodology and then to optimize its application in larger cohorts to provide a robust clinical solution.

Disclosures

Dr Pennell is a consultant to Siemens.

References


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