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EDITORIAL COMMENT

Quantification of Myocardial Perfusion and Myocardial Perfusion Reserve by Positron Emission Tomography and Cardiovascular Magnetic Resonance Imaging*

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Physiology and pathophysiology of myocardial perfusion regulation and of myocardial perfusion reserve. Because of the high energy demands of myocardial contraction, the heart is critically dependent on oxidative metabolism, and insufficient myocardial oxygen delivery (i.e., ischemia) results almost instantaneously in contractile and electrical dysfunction. Because myocardial oxygen extraction in the blood is already near maximal under resting conditions, myocardial perfusion is strongly correlated with myocardial oxygen consumption, and the principal mechanism for increasing oxygen delivery to the heart is by increasing myocardial perfusion (1).

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Under resting conditions, myocardial perfusion is autoregulated, thus independent of driving arterial pressure and adapted according to myocardial oxygen demand. This matching of perfusion with oxygen requirements occurs by control of myotonic tone of resistive pre-arterioles, which reduce capillary pressure and regulate perfusion to the required level. When myocardial oxygen demand increases due to higher cardiac workload, such as during exercise, the pre-arterioles relax under the influence of endothelial vasodilators, allowing perfusion to increase to meet higher oxygen demand. The magnitude of maximal perfusion increase during exercise or vasodilation is termed myocardial perfusion reserve (MPR). It is measured as the ratio of perfusion during maximal vasodilation, achieved by infusion of direct or indirect adenosine agonists, to resting perfusion, and averages approximately 3 to 5 in normal myocardium.

Presence of epicardial coronary stenosis results in arterial pressure drop downstream of the stenosis. Under resting conditions, reduction of pre-arteriolar resistance can compensate for this drop in arterial pressure, allowing capillary pressure and myocardial perfusion to remain normal, if stenosis severity is not too severe. However, this limits the ability to increase maximal perfusion during exercise or stress (2). Therefore, MPR decreases when stenosis severity increases beyond 50% luminal diameter reduction (3), yet with a wide variation between epicardial coronary stenosis severity and MPR measured in vivo (4). Indeed MPR depends not only on trans-stenotic pressure gradient and thus stenosis severity but even more on the ability of the pre-arterioles to dilate. Endothelial or microvascular dysfunction due to smoking, hypertension, diabetes, or dyslipidemia might reduce pre-arteriolar function and thus MPR independently of the presence of epicardial coronary stenosis. Hence, the ability to quantitatively measure stress myocardial perfusion and MPR would allow a more comprehensive understanding of chest pain syndromes in patients and, in particular, of microvascular dysfunction (5). Yet such quantification of MPR is not readily available in clinical practice. Indeed it requires the ability to quantity myocardial perfusion in absolute terms (i.e., in ml/min/g tissue) both during maximal vasodilation and at rest.

How can myocardial perfusion and perfusion reserve be quantified? In humans, positron emission tomography (PET) is currently considered the reference technique for quantification of myocardial perfusion and MPR. Unlike conventional nuclear imaging, PET has the unique ability to measure absolute radiotracer concentrations, allowing the estimation of absolute myocardial perfusion from dynamic images after bolus injection of either ^{15}O-water, ^{13}N-ammonia, or ^{82}Rb (6). These tracers diffuse into the myocardium in direct proportion to myocardial perfusion. ^{13}N-ammonia is subsequently trapped by metabolization into ^{13}N-glutamate. The behavior of these tracers can thus be described by 2- or 3-compartment models, respectively, and myocardial perfusion can be estimated by fitting myocardial against blood tracer concentration curves or by a simplified graphical approach termed "Patlak analysis." The main disadvantage of PET is the short half-life of the radioisotopes, requiring an onsite cyclotron or a ^{82}Rb generator for tracer production. Therefore, this technique has never seen widespread clinical usage.

Magnetic resonance perfusion imaging is more extensively available and allows for dynamic cardiac first pass perfusion imaging after injection of gadolinium (Gd)-based contrast agents with higher temporal and especially spatial resolution than PET. It would thus be an ideal technique for clinical assessment of stress myocardial perfusion and

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MPR. Yet it has several methodological shortcomings that need to be overcome to allow quantitative measurements of myocardial perfusion to be performed (7). Most importantly, magnetic resonance imaging (MRI) cannot directly measure contrast agent concentration. Although signal intensity increase on T1 weighted imaging sequences is roughly proportional to Gd concentration at low concentration, this relation becomes nonlinear for high Gd concentrations, resulting in tracer underestimation at high concentrations, a problem occurring particularly in the blood pool. To overcome this limitation, a double bolus injection protocol was proposed, in which the blood tracer curve is obtained from a first injection of diluted contrast and the myocardial curve is obtained from a second injection of more concentrated contrast (8). Another problem is that the currently available contrast agents have incomplete first pass extraction rate and variable extravascular distribution, especially in infarcted or fibrotic tissue. Therefore kinetic compartment models, such as used for PET, are less reliable to quantify perfusion for MRI than for PET. A more robust approach for quantification of myocardial perfusion by MRI is deconvolution of the myocardial against the blood signal intensity curve to a Fermi function tissue impulse response curve (9). By this approach the value of the Fermi curve at time $t = 0$ provides the estimate of myocardial perfusion.

Contribution of article. Because of the difficulties of quantifying myocardial perfusion by MRI, so far there have been only a few studies evaluating the accuracy of MPR measurements by MRI in humans with coronary artery disease (CAD). Therefore, the study by Morton et al. (10) in the present issue of the *Journal* makes an important contribution to the field. It compared measurements of absolute myocardial perfusion and of MPR by adenosine stress-rest perfusion MRI with a double bolus injection protocol and Fermi deconvolution against ^{13}N-ammonia PET with Patlak analysis in patients with suspected coronary disease before coronary angiography. The study demonstrated a good correlation between MPR estimates by MRI and PET, thereby validating the accuracy of MPR measurements by this MRI technique. Interestingly, however, individual resting and stress myocardial perfusion measurements did not correlate well among MRI and PET. There could be different explanations to account for this. First, the MRI and PET studies were performed at different times, and myocardial perfusion might have varied physiologically or due to changes in hemodynamic conditions over time. More likely, however, these differences reflect dissimilarities between the MRI and PET approaches to quantify perfusion, in particular the distinct tracer properties, model assumptions, and fitting methods as well as parameter constraints. Accordingly, we observed earlier that absolute myocardial perfusion estimates might differ for 2 PET tracers employing different models (11). The inter-method variation of myocardial perfusion likely cancelled out when MPR was computed from the ratio of rest to stress perfusion, explaining why MPR correlated better than absolute perfusion measurements among methods. Another important finding of the study by Morton et al. was that MPR by MRI had similar high diagnostic accuracy to detect significant CAD by coronary angiography than MPR by PET. This corroborates the clinical usefulness of adenosine stress MRI for noninvasive detection of CAD (12). Unfortunately, however, due to the limited number of subjects, the study could not demonstrate whether absolute quantification of perfusion or of MPR improves diagnostic accuracy for detection of CAD over visual analysis alone. Therefore we must wait for further studies to evaluate whether the efforts and intricacies required to quantify myocardial perfusion and MPR by MRI can be warranted by better diagnostic accuracy or greater prognostic value in patients with CAD.

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