A Novel 18F-Labeled Tracer for the Quantification of Myocardial Blood Flow and Infarct Size With Positron-Emission Tomography

Another Way to Avoid the Need of an On-Site Cyclotron

Paolo G. Camici, MD; Ornella E. Rimoldi, MD

Currently, nuclear imaging techniques can be used to diagnose coronary macrovascular and microvascular disease and to measure infarct size and left ventricular ejection fraction. Semiquantitative assessment of regional myocardial perfusion with single-photon emission computed tomography is a noninvasive, robust, and widely available method of assessing myocardial ischemia and has an established role in the clinical setting. A great number of studies have assessed the sensitivity and specificity of this technique for the detection of coronary artery disease (CAD), with coronary arteriography usually being used as the standard by which the accuracy of scintigraphy is judged. The main limitation of single-photon emission computed tomography perfusion imaging is that it provides only semiquantitative information on the regional distribution of myocardial blood flow (MBF). This is particularly relevant in conditions in which MBF and coronary flow reserve (CFR) are diffusely abnormal, (eg, in patients with hypertrophic and dilated cardiomyopathies).

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The ability to make quantitative measurements of MBF with positron-emission tomography (PET) allows determination of the functional significance of epicardial coronary lesions. In patients with single-vessel CAD, chronic stable angina, and no previous history of myocardial infarction (MI), CFR in response to a standard dose of dipyridamole was found to be markedly reduced in the myocardial regions subtended by the stenosed coronary artery compared with regions subtended by angiographically normal vessels. Using H215O or 13NH3 with PET, the relationship between stenosis severity, measured by quantitative coronary angiography, and its consequences on regional MBF and CFR has been described. Furthermore, the quantification of regional MBF has highlighted the impairment of CFR also in regions that are not subtended by a stenosed artery in patients with CAD elsewhere.

Another form of early (often preclinical) coronary disease affecting the microcirculation (small vessels <300 to 400 μm in diameter), which most often interests the entire left ventricle, may be demonstrated in patients with normal coronary angiograms. Because there is no technique enabling direct visualization of the coronary microcirculation in vivo, its assessment relies on the measurement of parameters, which reflect its functional status, such as absolute MBF and CFR.

Studies using PET for the noninvasive quantification of regional MBF in asymptomatic subjects with risk factors for CAD, such as hypercholesterolemia, essential hypertension, diabetes mellitus, and smoking, have provided evidence of how these risk factors translate into measurable damage to the coronary microcirculation in the absence of demonstrable stenoses of the epicardial arteries. In some cases, these abnormalities represent mere epiphenomena, whereas in others they represent important markers of risk or even contribute to the pathogenesis of myocardial ischemia, thus becoming therapeutic targets.

Because of their very short physical half-life (t1/2), both H215O (t1/2, 2 minutes) and 13NH3 (t1/2, 10 minutes) require an on-site cyclotron. Generator-produced 82Rb is a very appealing tracer for measurement of MBF, because it does not require an on-site cyclotron and has a very short t1/2 (78 seconds) that allows repeated measurements of MBF in the same session. Although several models have been proposed for quantification of regional MBF using 82Rb, they are limited by the heavy dependence of the myocardial extraction of this tracer on the prevailing flow rate and myocardial metabolic state. Therefore, quantification of regional MBF with 82Rb may be less accurate, particularly during hyperemia or in metabolically impaired myocardium.

Single-photon emission computed tomography with 99mTc-labeled tracers has been extensively validated for the assessment of both the territory subtended by the culprit artery and the extension of the final fixed defect, which is in close association with the fibrosis measured in explanted human hearts. Left ventricular ejection fraction, infarct size, and end-systolic volume measurements are strong predictors of 6-month mortality after MI, and it is possible to standardize the measurements across different centers. More than 5000 patients have been assessed in multicenter, randomized studies with infarct size as a surrogate end point to evaluate the impact of pharmacological/interventional treatments or the time to treatment. More recently, magnetic resonance has emerged as a valuable tool to measure the amount of scarred tissue, its transmural extent, and the functional sequelae. In patients with clinical features of CAD, but without a history
of MI, Kwong et al. have shown that even a small amount of gadolinium enhancement, probably indicating subclinical MI, carries a high cardiac risk. PET has the ability to identify viable and nonviable myocardium by imaging with the glucose analogue \(^{18}F\)2-fluoro-2-deoxy-D-glucose. Compared with single-photon techniques, PET offers superior spatial resolution and attenuation correction, and it allows absolute quantification of regional tracer uptake. Nevertheless, PET with \(^{18}F\)2-fluoro-2-deoxy-D-glucose is limited by the necessity to standardize glucose uptake by means of euglycemic hyperinsulinemic clamp, which prolongs the study duration.

The possibility to use a positron-emitting tracer that can accurately assess absolute MBF, infarct size, and left ventricular ejection fraction in the same scanning session and does not require an on-site cyclotron is obviously very attractive. In this issue of *Circulation: Cardiovascular Imaging*, Sherif et al. report on the use of the novel \(^{18}F\)-labeled PET perfusion tracer \(^{18}F\)-BMS747158-02 that they validated in rats for the assessment of infarct size. This novel tracer is an analogue of the insecticide pyridaben that binds the mitochondrial complex I of the electron transport chain with high affinity and shows good uptake in the heart due to its high density of mitochondria. This tracer has several promising features: a relatively long \(t_{1/2}\) (110 minutes), allowing distribution from a central cyclotron facility similarly to \(^{18}F\)-2-fluoro-2-deoxy-D-glucose; good image quality, as it emits a low-energy positron that travels a short distance in tissue before annihilation, providing a good contrast between the heart and the surrounding tissues that remains stable over time; and high extraction of \(^{18}F\) BMS747158-02 at first pass (3.1% of injected dose per gram), not affected at higher flow rates, hinting at linearity between tracer uptake and perfusion.

The latter feature should enable accurate quantification of MBF. Sherif et al. used \(^{18}F\)-BMS747158-02 for quantification of infarct size in rats with either permanent (24 hours) or transient (30 minutes) ligation of the left circumflex coronary artery, followed by 24 hours of reperfusion. The tracer uptake clearly delineated the borders of the defects and was in good agreement with the anatomic infarct size measured by planimetry ex vivo.

Gating was applied to measure left ventricular volumes and systolic function. However, determination of volumes by \(^{18}F\)-BMS747158-02 was hampered by difficulty of determining left ventricular contours in the absence of reliable tracer uptake when a transmural MI was present. This promising tracer still has a long way to go before clinical application can be envisaged. In humans, the infarct location is not limited to the territory of 1 coronary artery, and multiple patchy infarcts can be present simultaneously; an accurate infarct quantification in this case scenario has to be proven. Standardization and repeatability of measurement of infarct size and ventricular remodeling has become essential in the evaluation of the outcome of cell therapy after acute MI. Will a PET tracer like \(^{18}F\) BMS747158-02 perform better than magnetic resonance?

Finally, the relatively long \(t_{1/2}\) of \(^{18}F\) BMS747158-02 on one hand has the advantage of overcoming the need for an on-site cyclotron but on the other hand would make it very difficult to measure resting and stress MBF in a single-scan session.

**References**


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**Disclosures**

None.
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