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JACC: CARDIOVASCULAR IMAGING VOL. 4, NO. 9, 2011
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ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2011.07.002

EDITORIAL COMMENT

Absolute Myocardial Blood Flow

Emerging Role in Coronary Pathophysiology and Clinical Disease*

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Recent studies have increased interest in quantifying absolute myocardial blood flow (MBF) noninvasively, particularly in maximally vasodilated coronary vascular beds. Reductions unrelated to epicardial coronary artery disease have become an important tool in the identification of microvascular dysfunction. Sequential measurements have provided useful insights into microvascular pathophysiology and treatment. Novel therapies designed to stimulate angiogenesis and myocardial regeneration may exert their effect via improvement in microvascular flow.

See page 990

In contrast to values of coronary flow reserve (CFR), values of vasodilated absolute MBF are unaffected by levels of "resting" flow. They do, however, vary directly with changes in arterial pressure and inversely with changes in heart rate (1). In healthy normal individuals, vasodilation can increase resting absolute MBF 4- to 5-fold, reaching levels of ~4 ml/g/min with only modest changes in heart rate and arterial pressure. Thus, maximum vasodilation uncouples the usual close relationship between myocardial oxygen demand and coronary flow, and usually increases absolute MBF above the level needed for fairly vigorous physical activity.

Positron emission tomography (PET) has traditionally been the noninvasive standard for quantifying absolute MBF (2). Magnetic resonance, computed tomographic, and echocardiographic approaches are now being used in some laboratories. Absolute MBF can also be measured using dynamic single-photon emission computed tomography (3), but cameras with sufficient speed and count sensitivity are not yet widely available.

Absolute MBF and perfusion scans in coronary artery disease. Routine myocardial perfusion scans identify only relative differences in regional tracer activity and assume the presence of at least 1 normally perfused area to which others can be compared. Measurements of absolute MBF can aid in interpretation in patients with coronary artery disease, for example, when a normal or near-normal stress scan may reflect an unappreciated global reduction in flow in a patient with diffuse triple vessel disease. If hemodynamically important lesions are indeed widespread, vasodilated absolute MBF should be reduced globally.

Regional perfusion defects developing during pharmacological vasodilation present more frequent interpretive issues. Because myocardial oxygen demand increases only modestly, ischemia is infrequent. In the absence of ischemia, measurements of vasodilated absolute MBF add information concerning residual flow reserve, including limitations related to microvascular dysfunction as well as differing degrees of epicardial stenosis. Hajjiri et al. (4) have reported that ^{13}N-ammonia measurements of adenosine-stimulated absolute MBF are superior to quantitative measurements of relative tracer retention in identifying coronary artery disease, and that a single measurement of vasodilated absolute MBF is adequate for this purpose. The possibility that the magnitude of reduction in vasodilated absolute MBF can provide useful information about disease severity merits exploration.

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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JACC: CARDIOVASCULAR IMAGING, VOL. 4, NO. 9, 2011
SEPTEMBER 2011:999–1001

PET measurements of absolute MBF during dipyridamole-induced vasodilation. In this issue of *iJACC*, Johnson and Gould (5) review their laboratory's experience in quantifying absolute MBF with PET in an attempt to define low-flow threshold values of absolute MBF and CFR that are associated with regional ischemia during dipyridamole-induced vasodilation. A total of 1,674 perfusion scans and absolute MBF measurements were performed in 1,370 patients, primarily using ^{82}Rb. Responses were classified into 3 categories:

1. "Definite" ischemia: studies showing a new or worsened scan defect during vasodilation accompanied by either >1-mm ST-segment depression or angina requiring pharmacological treatment.
2. "Indeterminate" responders: studies showing at least 1 of these abnormalities during vasodilation. The large majority (71%) represented new or worsened scan defects not accompanied by ST-segment depression or angina.
3. "No" ischemia: studies showing none of the aforementioned abnormalities and no scintigraphic evidence of myocardial scar.

Unlike studies using region-of-interest analysis, absolute MBF values were computed on a per-pixel basis (see text of reference [5] for details). Results for "worst" flow and CFR referred to individual pixels and were, therefore, less than average values for an entire perfusion defect or reference area. Additionally, the anatomical location of a "worst" pixel could differ between rest and vasodilator stress.

Definite ischemia was identified in only 12% of studies; 18% fell into the indeterminate group, 20% showed myocardial scar, and the remaining 50% constituted the no ischemia group. Worst vasodilated absolute MBF averaged 0.47 ± 0.26 ml/g/min, 0.81 ± 0.47 ml/g/min, and 1.56 ± 0.54 ml/g/min in the definite, indeterminate, and no ischemia categories.

The definite and no ischemia groups were sharply separated at a vasodilated worst absolute MBF cutoff of 0.91 ml/g/min, with an area under the corresponding receiver-operator characteristic curve of 0.98. Flows in indeterminate cases showed greater overlap with the no ischemia group, although the receiver-operator characteristic curve for a worst absolute MBF cutoff of 1.12 ml/g/min still had an area under the curve of 0.86.

Separation between cases of definite ischemia and indeterminate responders was less clear: 66% (198/301) of worst stress flows in indeterminate responders fell below the 0.91 ml/g/min cutoff for definite versus no ischemia. The worst flow cutoff for optimal separation between definite and indeterminate groups (0.52 ml/g/min) did not differ appreciably from the average worst flow in cases of definite ischemia (0.47 ml/g/min).

Although this study provides information about worst per-pixel absolute MBF in an unusually large number of patients, the authors caution that the data "will require further extended study before understanding their clinical relevance." When a vasodilation-induced perfusion defect is accompanied by ST-segment depression or clear-cut angina, a worst absolute MBF ≤0.91 ml/g/min can be expected in >90% of cases. ST-segment depression and/or angina are infrequent when worst vasodilated absolute MBF exceeds 1.12 ml/g/min. However, the specificity and positive predictive accuracy of absolute MBF for identifying vasodilation-induced scan defects that do produce ischemia are affected adversely by the overlap of worst per-pixel values in definite and indeterminate cases. As the authors discuss, decisions concerning further diagnostic evaluation depend on the size of the perfusion defect as well as the severity of reduction in absolute MBF and other clinical factors.

The present findings were likely influenced, albeit to an unknown degree, by drug treatment at the time of study. As noted previously, values of absolute MBF during maximum vasodilation are influenced by absolute levels of heart rate and blood pressure, both of which can be altered by agents such as beta blockers, calcium blockers, and nitrates. Similarly, statins and other agents may affect endothelial-dependent components of maximum vasodilation.

As the authors also point out, cardiac PET quantifies average transmural flow and is ordinarily unable to distinguish subendocardial from subepicardial perfusion. Subendocardial flow is normally less than subepicardial flow during maximum vasodilation, and the magnitude of the difference can increase during ischemia (1). Thus, the separation between cases of definite ischemia and those with indeterminate clinical features would likely be enhanced if subendocardial absolute MBF could be quantified selectively. Because of its superior resolution, magnetic resonance imaging is being investigated actively in this regard. Limitations requiring continuing attention include subendocardial artifacts, less-than-complete ventricular coverage, and a nonlinear relationship between signal intensity

and gadolinium tracer concentration that assumes greater importance as flow increases (6).

Methodological standardization. Noninvasive measurements of absolute MBF in individual laboratories can be expected to contribute usefully in continuing studies of coronary pathophysiology and selected clinical issues. As Gewirtz (7) has emphasized, however, multi-institutional PET studies remain limited by differences in tracers, kinetic models, technical methodology, image analysis, and pharmacological vasodilating agents. For example, reported PET stress flows in normal individuals vary from 1.86 ± 0.27 to 5.05 ± 0.90 ml/g/min, with a 27% weighted average coefficient of variation for single measurements (Table 4 in reference [8]). Similar multi-institutional information for other imaging modalities is limited but equally important. Options for improving methodological standardization deserve careful study and may prove an important determinant of the ultimate clinical utility of absolute MBF measurements.

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Key Words: absolute myocardial flow ■ myocardial perfusion scans ■ positron emission tomography ■ vasodilated coronary flow.