EDITORIAL

"Mismatch" in regional myocardial perfusion defects during exercise and pharmacologic vasodilation: A noninvasive marker of epicardial vasomotor dysfunction?

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In this issue of the journal, Verna et al[1] report on an association between the extent of epicardial endothelial dysfunction in response to acetylcholine stimulation and the degree of exercise-induced regional myocardial perfusion defect as determined by single photon emission tomography (SPECT) and technetium 99m tetrofosmin in patients without flow-limiting epicardial lesions. Investigations by Zeiher et al[2] were first to demonstrate that endothelial dysfunction of the coronary microcirculation may be paralleled by exercise-induced regional myocardial perfusion defects in patients without flow-limiting artery lesions. The current investigation is in accord with these earlier observations[2] but extends them now to a moderate association between epicardial endothelial dysfunction in response to intracoronary acetylcholine stimulation and the degree of exercise-induced perfusion defect. Such findings may indeed suggest that, even in the absence of focal coronary artery lesions of greater than 50% diameter stenosis, functional abnormalities of the epicardial conductance vessels may also affect myocardial perfusion during bicycle stress exercise. Thus current and previous observations[3-6] indicate that coronary flow increases during bicycle stress exercise or during pharmacologic vasodilation are likely to reflect flow-mediated alterations of the epicardial conduit arteries and the coronary arteriolar resistance vessels together, rather than being representative of vasomotor function of the arteriolar vessels alone.[4,7-12] Notably, the authors "normalized" the degree of exercise-induced perfusion defect to the corresponding extent of perfusion defect during pharmacologically induced vascular smooth muscle cell relaxation. This was performed by calculating the difference between the extent of the perfusion defects during exercise and pharmacologic vasodilation. The difference in stress-induced perfusion defects or, as the authors suggest, a so-called perfusion mismatch during different forms of vasomotor stress significantly correlated with the extent of epicardial endothelial dysfunction ($r = 0.50$, $P < .04$).[1] The latter association may emphasize that abnormalities in epicardial vasomotor function may indeed account for or contribute to exercise-induced perfusion defect in patients without flow-limiting coronary artery lesions.

These new findings of Verna et al[1] may add to the previous observations of Gould et al,[3,5] which described a relationship between diffuse epicardial coronary artery disease (CAD) and longitudinal scintigraphic perfusion defects during dipyridamole stimulation. With positron emission tomography (PET) measurements of myocardial blood flow in milliliters per gram per minute during pharmacologic vasodilation or sympathetic stimulation to cold pressor testing (or both), a relative longitudinal decrease in myocardial blood flow from the base to the apical portion of the left ventricle was also observed in patients with risk factors for CAD.[13,14] The mechanism underlying this stress-induced longitudinal perfusion gradient or heterogeneity in left ventricular myocardial perfusion is most likely related to downstream fluid dynamic consequences of functional or structural alterations of the coronary circulation.[15-20] According to the Hagen-Poiseuille equation,[15-17] intracoronary resistance is determined by the length of the coronary vessel segment and the flow velocity, but it also depends inversely on the fourth power of the vessel diameter. Therefore even minor functional or structural alterations of the coronary circulation may interfere with a flow-mediated adjustment of the vessel diameter to higher

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Supported by research grant HL 33177 from the National Heart, Lung, and Blood Institute, Bethesda, Md.

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J Nucl Cardiol 2007;14:769-74.
1071-3581/$32.00

doi:10.1016/j.nuclcard.2007.09.009

flow velocities.[15] The latter interference[15,20] may lead to a progressive decline in intracoronary pressure and, hence, to a progressive decrease in myocardial perfusion in the base to the apex direction of the left ventricle.[3,5,6,13,14,21]

As previous invasive investigations have shown,[9,18] increases in coronary flows due to pharmacologic vasodilation of the coronary arteriolar resistance vessels are normally associated with a flow-mediated and, thus, endothelium-dependent vasodilation predominantly at the site of the epicardial artery. In the presence of endothelial dysfunction, however, pharmacologically induced increases in coronary flows do not translate into a flow-mediated increase in epicardial diameter, and therefore the vessel diameter remains virtually unchanged.[9,22] The abnormal vasomotor response to exercise stress, however, may actually differ from the response during pharmacologic vasodilation in that it may also cause a sympathetically mediated coronary vasoconstriction.[23-26] It follows then that, in the absence of flow-limiting epicardial lesions, myocardial perfusion defects during exercise stress are possibly related to an impairment of flow-mediated vasodilation resulting from coronary endothelial dysfunction and, at the same time, to a decrease in coronary artery diameter as a result of a sympathetically mediated contraction of the vascular smooth muscle cells. In contrast, myocardial perfusion defects during pharmacologically induced flow increases are more likely to be related predominantly to CAD-induced structural alterations of the arterial wall, apart from the presence of a functional endothelial abnormality, and thus reflecting a relative anatomic stenosis.[3,5] Such consideration may provide some rationale for the current observations of Verna et al[1] that the extent of the myocardial perfusion defect was greater during exercise than during pharmacologic vasodilation. A sympathetically mediated vasoconstriction of a coronary stenosis during exercise, as Hess et al[23] have shown, may account for more severe and larger perfusion defects during exercise than during pharmacologic vasodilation. This functional component, which has an additive effect on the structural stenosis, would then correlate to the endothelium-related functional disturbance as elicited with acetylcholine in the current study.[1] The latter angiographic observations of Hess et al[23] may also explain the observed larger perfusion defects during exercise than during dipyridamole stimulation as determined recently by nitrogen-13 ammonia PET,[27] which deserves further investigation.

Similarly, SPECT-determined myocardial perfusion during exercise manifested in greater, more severe and reversible perfusion defects than during dipyridamole stimulation.[28-31] Comparative investigations with exercise and adenosine stimulation, however, did not always demonstrate a difference in defect size.[28,31] For example, in a study conducted by David et al,[29] only 45% of patients had larger SPECT-determined regional perfusion defects during exercise than with dipyridamole. Conceptually, if increases in heart rate and in blood pressures as a result of sympathetic stress, as previous investigations have shown,[32] are related to increases in serum norepinephrine concentrations as an index of sympathetic stimulation, then an association between an increase in heart rate and exercise-induced myocardial perfusion defects should be observed, which would indeed indicate that the degree of exercise-induced perfusion defects is related to the extent of the sympathetically mediated coronary vasoconstriction during exercise.[23] Indeed, David et al[29] observed that larger exercise defects were realized in those patients with heart rate increases of greater than 60 beats/min during exercise from rest than in those with exercise-induced lower heart rate increases ($<$60 beats/min). It is noteworthy that, in the study of Chow et al,[27] larger and more severe perfusion defects during exercise than during dipyridamole stimulation were more obvious in patients with mild to moderate perfusion defects during dipyridamole. The reason for this observation remains uncertain but is possibly related to less advanced CAD-induced vessel stiffness in these patients as possibly reflected by mild to moderate perfusion defects during dipyridamole, where the exercise-induced coronary vasoconstriction may still predominate and cause a larger and more severe perfusion defect. In this regard, a predominance of the functional vasoconstrictor component may dominate, for example, in mild CAD or, as shown in studies by Zeiher and colleagues, as well as by other authors,[7,9,19,20,22,33-36] in minor, nonsignificant CAD lesions, and it might give rise to "false-positive" scintigraphic perfusion imaging findings only when compared with coronary angiographic findings.[5,6,21] For the same reason, as several studies have suggested,[34,37-42] endothelial dysfunction or exercise stress–induced perfusion defects (or both) contain more predictive information on CAD progression and future cardiovascular events than findings on coronary angiography alone. On the other hand, as proposed by Gould et al,[5,21] a PET-determined longitudinal perfusion gradient or defect during pharmacologic vasodilation may identify early diffuse CAD. Thus, myocardial perfusion defects during pharmacologic vasodilation are likely to be more closely associated with the structural change in the coronary vessels as noted on coronary angiography.[3,5] This may also accord with the findings of Nishimura et al,[43] who observed larger perfusion defects during adenosine stimulation than during exercise thallium 201 SPECT. Conceptually, it is possible that in the latter population studied,[43] patients had more advanced focal coronary artery lesions ($\geq$70%-80%

diameter stenosis) or diffuse CAD (or both), where an exercise-related and sympathetically induced vascular smooth muscle cell contraction may not effectively translate into an additional coronary vasoconstriction and, thus, may not cause larger and more severe perfusion defects during exercise than during adenosine stimulation. The emerging new concept, however, in which scintigraphic perfusion imaging may delineate the continuous range from early CAD-induced functional or structural alterations of the coronary circulation to severe focal stenosis, might also explain the less-than-optimal specificity as reported in several studies that compared scintigraphic myocardial perfusion imaging with coronary angiography, when a significant coronary artery lesion was defined as 50% diameter narrowing or greater.[44-48]

Taken together, although perfusion defects during dipyridamole stimulation may predominantly reflect the structural stenosis,[5] the exercise study most likely demonstrates the effects of both coronary structural and functional abnormalities on myocardial perfusion.[1] This contention might explain the findings of Verna et al[1] and the proposed concept of a so-called mismatch in myocardial perfusion defects during different forms of vasomotor stress. In this setting, a greater perfusion defect during exercise stress than during dipyridamole stimulation (positive ratio of exercise to dipyridamole-induced perfusion defects) may identify predominantly early functional abnormalities of the coronary circulation, whereas the inverse (negative) ratio could in fact denote more CAD-induced structural changes of the arterial wall.[31,49] Although this consideration may be intuitively correct, it needs direct confirmation of "cause and effect" through prospective clinical investigations. As the authors mention, however, it remains unclear how their approach to assess myocardial perfusion combined with different forms of vasomotor stress may distinguish between exercise-induced perfusion defects resulting from flow-limiting epicardial stenosis and those without them.[1] Other variables such as stress-induced typical angina pectoris and significant ST-segment depression, which are frequently associated with stress-induced myocardial perfusion defects underlying a flow-limiting epicardial stenosis, could provide further important diagnostic information.[50] Although the mean sensitivity and specificity of exercise stress–induced ST-segment depression in the detection of flow-limiting epicardial stenosis of 63% and 74%, respectively, in several studies[51-54] are rather low, such information could possibly add useful information to SPECT perfusion imaging to differentiate between early stages of CAD-induced functional or structural abnormalities and an advanced focal flow-limiting epicardial stenosis. Another possibility is to apply multidetector-row computed tomography (MDCT) in the noninvasive evaluation of coronary morphology, which could add more definite information,[55-60] at the expense of a further increase in non-negligible ionizing radiation exposure.[61] Applying electrocardiography-triggered tube modulation, however, can lower the radiation dose to 4.3 mSv,[62] and further efforts are being made to reduce the radiation exposure of MDCT without compromising the diagnostic accuracy.[63] Future cardiac imaging protocols could implement MDCT–coronary angiography to identify the morphology and structure of the arterial wall in early as well as more advanced stages of the CAD process and its downstream effects on scintigraphically measured myocardial perfusion. With this approach, the combined application of SPECT-MDCT or hybrid SPECT-MDCT scanners[45,58,64-67] could expand the diagnostic scope of conventional SPECT perfusion imaging not only to identify flow-limiting epicardial lesions but also to detect and characterize early CAD-related alterations in coronary function and morphology. Because early alterations in function or morphology of the coronary arterial wall may provide important predictive information for future cardiovascular events, in addition to that derived from traditional coronary risk factor assessment,[45,68,69] an improvement in altered coronary function or morphology in developing CAD as a result of preventive medical intervention has awakened a general interest.[70,71] Whether medical interventions tailored to normalize early abnormalities in coronary function and morphology also mitigate an improved clinical outcome in individuals with subclinical or clinically manifest CAD remains to be established. The assessment of alterations in coronary function and morphology by SPECT/PET and MDCT, however, could be promising to successfully guide preventive medical intervention in CAD patients.

The investigation by Verna et al[1] adds to a new evolving concept that scintigraphic myocardial perfusion with SPECT or PET may identify and characterize the continuous CAD process from early alterations in coronary function and morphology to anatomic flow-limiting epicardial stenosis.[3,5,6,13,14] Their investigation suggests that myocardial perfusion imaging by means of SPECT combined with different forms of vasomotor stress, such as bicycle exercise and pharmacologic vasodilation, may be a unique tool by which to identify early changes in coronary function and morphology, providing important diagnostic and prognostic information.[3,6,40,45,72] The validity and value of the latter approach to assess noninvasively CAD-related early functional and structural abnormalities of the arterial wall, however, need to be established in further clinical investigations.

Acknowledgment

The authors have indicated they have no financial conflicts of interest.

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