Editorial: Noninvasive Quantification of Regional Myocardial Blood Flow: Assessment of Myocardial Perfusion Reserve and Collateral Circulation

This month's issue of the *Journal of Nuclear Medicine* contains two reports on the noninvasive assessment of regional or global myocardial perfusion reserve in patients with left ventricular hypertrophy (LVH) (*1*) and in patients with coronary artery disease (CAD) and collateral blood flow (*2*). Both reports employ positron emission tomography (PET) and positron emitting tracers of myocardial blood flow. Coronary flow or myocardial perfusion reserve have been determined previously with a number of invasive as well as noninvasive but often technically demanding techniques such as thermodilution and inert gas clearance, intracoronary Doppler catheters, and ultrafast computed tomography (*3–5*). Most studies demonstrated an average five-fold increase in coronary flow velocity or myocardial perfusion in normal subjects in response to potent vasodilators as, for example, dipyridamole or papaverine. Coronary artery disease markedly attenuates such flow increases. Of interest is that similar reductions in coronary flow or myocardial perfusion reserve are also present in patients with LVH even when the large epicardial vessels are free of disease. Such impairment appears to explain the presence of ischemia and its clinical manifestations in LVH (*6,7*), although the mechanism of the reduced flow reserve remains uncertain. Maximal achievable flows may, for example, remain normal, while resting blood flows are elevated (*8, 9*), so that the coronary flow or myocardial perfusion reserve as the ratio of maximum over resting blood flow is decreased. The observation of an 8.5% reduction in myocardial perfusion reserve in patients with LVH and without evidence of CAD as reported by Goldstein et al. (*1*) is consistent with these earlier findings. While using a similar approach but evaluating regional rather than global myocardial blood flow, Demer et al. (*2*) report a 15-percent decrease rather than increase in regional tracer concentrations after dipyridamole in collateralized myocardial regions in patients with severe CAD.

The protective effect of collateral blood flow on myocardium subtended by stenosed coronary arteries has long been recognized (*10*). For example, patients with well-developed collaterals may have significantly higher 10-yr survival rates after coronary occlusion than patients with poorly-developed collaterals (*11*). Further, collateral flow may be adequate to maintain normal levels of myocardial blood flow and contractile function at rest, although in most circumstances it will be inadequate during conditions of increased demand as, for example, during physical stress. As Demer and colleagues discuss, increases in the coronary flow velocity may result in a redistribution of the sites of major resistance points or pressure gradients within the coronary circulation and, thus, cause an actual decrease or "coronary steal" rather than an increase in regional myocardial tissue blood flow (*2*). Thus, coronary steal may cause the previously described dipyridamole-induced wall motion abnormalities (*12*) or, as reported in this manuscript, electrocardiographic and clinical evidence of acute myocardial ischemia (*2*).

Common to both reports is the use of PET and short-lived positron emitting tracers of blood flow as for example, the generator-produced rubidium-82 or the cyclotron produced nitrogen-13 ammonia. Rather than resorting to dynamic image acquisition and the use of tracer kinetic models for quantifying regional myocardial blood flow in ml blood per minute per gram myocardium as is now possible (*13,14*), both studies determine the regional myocardial tracer tissue concentrations as a function of the total amount of tracer injected at baseline and after pharmacologic vasodilation. Thus, the approach does not measure regional myocardial blood flow per se but rather provides an estimate of the dipyridamole-induced increase in global or regional myocardial blood flow or the ratio of hyperemic to control flow.

The investigators equate an ~1.5-fold increase in myocardial tracer tissue concentrations with the previously reported five-fold increase in myocardial blood flow (*9,15,16*). Different from these normal values, Goldstein et al. report an only 1.06 times increase in patients with LVH and, thus, a markedly reduced global myocardial perfusion reserve. Similarly, Demer et al. observes only a 1.27-fold increase in patients with CAD but a 15-percent decrease in regional tracer tissue concentrations in collateralized myocardial territories and refer to this decline as "PET steal."

Despite its practicality and clinical attractiveness, the approach as employed by the authors may be hampered by a number of potentially serious shortcomings. It entails several assumptions, which may not hold for all study conditions. The calculation of "perfusion ratios" does not correct for the fact that the first-pass extraction fractions (E) of both tracers of blood flow are less than

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unity and decrease nonlinearly with higher flows (*17*). This decline in E accounts to a large extent for the markedly lower than expected dipyridamole-induced increase in tracer-tissue concentrations and, thus, in the hyperemia-to-baseline ratios of only 1.5 or less. Second, the approach assumes that cardiac output does not increase. Estimation of regional myocardial blood flow or, more importantly for these studies, of its changes in response to dipyridamole employs the "fractionation principle" (*18*). The tracer distributes throughout the body in proportion to the distribution of cardiac output. The tracer-tissue concentration in a given myocardial region of interest (ROI) therefore represents the fraction of the total cardiac output to that region of interest. If dipyridamole were to selectively increase coronary blood flow and, thus, flow to the myocardial ROI, then changes in regional myocardial tracer-tissue concentrations could be ascribed only to changes in myocardial blood flow. However, dipyridamole has been observed to increase cardiac output by an average of 1.5 to 1.6 times (*19–21*). Because the authors equate in their approach the total dose of activity with the total cardiac output, the increase in cardiac output blunts estimates of absolute regional flow increases based on the fractionation principle. If for example the fraction of cardiac output to the coronary circulation averages at baseline ~5%, coronary vasodilation by dipyridamole with a five-fold increase in coronary blood flow would increase this fraction to ~25% provided that the drug selectively vasodilates only the coronary circulation. However, a 50- to 60-percent increase in cardiac output lowers the fractional cardiac output to the coronary circulation by a factor of 0.4–0.5 or 10–12.5%. Thus, the systemic vasodilatory effect further reduces the estimated flow increase as determined by the fractionation principle.

Obviously, fixed values for corrections of the increasing cardiac output as well as the decline in tracer first pass extractions could be introduced. Use of such values would be based on the following assumptions:

1. The increase in cardiac output is constant for all individuals and different patient groups.
2. Because of the nonlinear relationship between E and myocardial blood flow, E at rest is known and rest blood flows are relatively constant.
3. Dipyridamole consistently induces a maximum coronary vasodilatory response.

None of these assumptions seems to be entirely valid. Significant intergroup differences in hemodynamic changes between normals and LVH patients following dipyridamole infusion in the report by Goldstein et al. do suggest that responses in cardiac output were different, which could have affected the observed markedly depressed myocardial perfusion reserve. Different responses in cardiac output have indeed been demonstrated in animal experiments (*22*) and in patients (*19*). Furthermore, there is also evidence, based on studies with intracoronary flow velocity probes, that changes in coronary flow velocity after dipyridamole may vary considerably between patients and are not necessarily maximum when compared to higher doses of dipyridamole or of intracoronary papaverine (*20*).

Additional limitations pertain to regional changes in blood flow. Radioactivity concentrations determined from myocardial ROIs are subject to the partial volume effect (*23*). True tracer-tissue concentrations are underestimated if the thickness of the imaged object or of the myocardial wall is less than twice the spatial resolution of the imaging device. The degree of underestimation increases nonlinearly as wall thickness declines. If for example coronary steal causes ischemic wall motion abnormalities, then the loss of systolic thickening results in an average lower wall thickness and in an apparent decline in tracer tissue concentrations. Even if coronary steal leads to only a subendocardial fall in blood flow, while epicardial blood flow actually increases and, thus, transmural flow remains unchanged, the transmural redistribution of blood flow may result in an apparently thinner wall and, thus, again lead to a partial volume related underestimation of true blood flow (*24*). Because of these shortcomings, Demer et al. appropriately referred to their observations as "PET steal" rather than "coronary steal." It is of interest that a more recent study failed to detect a true decrease in regional myocardial blood flow in collateral territories. These studies employed quantitative measurements of regional myocardial blood flow using dynamic PET imaging and oxygen-15-labeled water (*25*).

The studies presented in this issue of the *Journal* on dipyridamole-induced changes in global and regional myocardial blood flow are clearly intriguing and represent a new look with a new technology at a well established or suspected phenomenon. The ease with which these measurements can be obtained is intriguing and renders the approach clinically practical. Nevertheless, limitations of this approach emphasize the importance to critically and carefully evaluate findings in order to avoid erroneous conclusions. On the other hand, newly available noninvasive as well as invasive methods for quantifying regional myocardial blood flow (*13,14,26*) though tedious and time-consuming, are likely to more accurately delineate true changes in myocardial perfusion reserve and to elucidate mechanisms that are operational in LVH in terms of baseline and maximum achievable flows and their relationship to ischemia.

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