EDITORIAL COMMENT

Contractile Reserve and Coronary Blood Flow Reserve in Collateral-Dependent Myocardium*

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Numerous studies in recent years have clearly demonstrated that viable myocardium with contractile dysfunction maintains a contractile reserve that can be unmasked by inotropic stimulation, such as by the infusion of low doses of dobutamine. Hence, low-dose dobutamine echocardiography (LDDE) has become firmly established as a diagnostic tool in patients with coronary artery disease (CAD) and left ventricular (LV) dysfunction as a means to differentiate hibernating and stunned myocardium from irreversibly damaged myocardium. The available data indicate that function and flow remain coupled in reversibly dysfunctional myocardium, so that the increases in myocardial oxygen demand associated with inotropic stimulation are accompanied by increases in myocardial perfusion. Indeed, preserved coronary blood flow reserve is believed to be a requisite for contractile reserve.

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In stunned myocardium arising from reperfusion after coronary occlusion, coronary blood flow reserve is usually maintained in response to increases in myocardial demand, although microvascular stunning may attenuate vasodilator responsiveness. Similarly, in hibernating myocardium, coronary blood flow is reduced at rest and blood flow reserve is present but attenuated (1–3), which has been measured directly in patients with radiolabeled microspheres and quantitative positron emission tomography (PET). Such attenuated coronary blood flow responsiveness has also been demonstrated quantitatively by PET in myocardium that is totally dependent on collateral blood flow (4,5). This augmentation of flow in hibernating myocardium in response to vasodilator stimuli (1,4,5) and increases in myocardial demand (2,5) averages 40% to 50% (significantly lower than that of normal myocardium) and may be considerably lower in individual patients. Standard myocardial perfusion imaging using single photon emission tomography (SPECT), which has reduced resolution and sensitivity compared with PET and lacks the quantitative capabilities of PET, may identify augmented myocardial blood flow in response to inotropic stimulation in many patients with hibernating myocardium, but it is unlikely that SPECT will be sensitive enough to detect those patients with more subtle increases in blood flow, as might occur in patients with a relative paucity of collateral channels.

As hibernating myocardium represents a delicate balance between flow, function and viability, it is also quite likely that the increased demands of inotropic stimulation in some patients will overwhelm the limited flow reserve and result in myocardial ischemia. This may explain, in part, the reduced sensitivity of LDDE to detect viable but underperfused myocardium compared with perfusion imaging (6), because the myocardial regions with the most reduced basal blood flow and exhausted blood flow reserve may not be able to increase contractility at even low levels of demand. This also explains the common finding of a biphasic response to dobutamine (7,8), in which low dose dobutamine elicits an increase in regional systolic wall thickening, but higher doses exhaust flow reserve and produce ischemia, resulting in a reduction in wall thickening toward baseline values.

A more controversial concept is whether inotropic stimulation can cause ongoing augmentation of transmural systolic function after exhaustion of flow reserve and during active ischemia, particularly in the subendocardial regions. Experimental models of short-term myocardial hibernation indicate that dobutamine may produce subendocardial ischemia while continuing to increase transmural wall thickening (9,10) and that this may even lead to subendocardial necrosis (10). Hence, caution has been raised about the use of dobutamine for diagnostic testing in patients with critical coronary artery stenoses and for inotropic support during acute myocardial infarction (3). One might also consider the potential hazards of inotropic support for the short-term management of patients with decompensated heart failure, the majority of whom have CAD (11).

Evidence in support of such concern is provided by quantitative PET studies in patients with viable myocardium with reduced perfusion and systolic function. Sambuceti et al. (5) reported augmented myocardial blood flow in patients with collateral-dependent myocardium in response to both increased demand (atrial pacing) and vasodilator stimuli (dipyridamole). However, the magnitude of the increased in flow varied considerably among patients, and transmural blood flow actually decreased in some patients in response to atrial pacing, with the likelihood of an even greater decrease in the subendocardial layer. Reduced perfusion during the increased demand of tachycardia presumably represents ischemia. Reduced transmural vasodilator reserve in that study was most evident in patients with poorly developed compared with those with well

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engineered collateral channels visualized at angiography (5). Sun et al. (2) demonstrated that increase in contractility induced by dobutamine is associated with either no change or a decrease in quantitative glucose use in normally perfused regions of patients with CAD and LV dysfunction, as it is in normal control subjects. However, in viable regions characterized under basal conditions by reduced wall motion and reduced blood flow with metabolism-blood flow “mismatch,” the increases in wall motion and blood flow during dobutamine were associated with an increase in glucose use. Although this effect could represent a metabolic perturbation resulting from altered beta-receptor density or function in hibernating myocardium (which has not been previously described), this pattern also fits the well-established metabolic fingerprint of acute myocardial ischemia (12).

The study of Barilla et al. in this issue of the Journal (13) adds further support to the concept that inotropic stimulation may augment contractile function in reversibly dysfunctional myocardium without an appropriate increase in transmural myocardial blood flow. Among patients with reduced regional myocardial function and perfusion (as assessed by Tc-99m-sestamibi SPECT) after acute myocardial infarction, those with well-developed collateral vessels visualized at angiography manifested significant increases in myocardial blood flow and contractile function during LDDE, which translated in the majority of patients into improvements in wall motion after myocardial revascularization. This finding would be expected. The important and unique observation was that many regions with poorly developed collateral vessels also manifested contractile reserve with LDDE, but with no measurable flow response; most patients showed recovery of both regional wall motion and myocardial blood flow reserve after revascularization.

The patients studied by Barilla et al. seem to represent a spectrum of acute or short-term myocardial hibernation (14) rather than pure stunning, because they had a critical stenosis (>90% luminal narrowing) in the infarct-related artery with reduced blood flow at rest and the improvement in wall motion was not spontaneous but was accomplished only after revascularization. There are several implications of their findings. First, contractile responsiveness to dobutamine may occur in this setting without an augmentation in transmural flow, suggesting a dissociation of the flow-function relationship, exhaustion of coronary flow reserve and at least subendocardial ischemia. These data seem to contradict previous PET studies indicating that hibernating myocardium has preserved but attenuated blood flow reserve to inotropic stimuli (2,4,5). Although this apparent difference may be explained by the selection of patients with short-term hibernation by Barilla et al. rather than patients with chronic LV dysfunction (which was the case in the previous PET studies), this difference may also be explained by technical issues, noted in the following section. From a more practical perspective, the current data also raise the possibility that LDDE may have greater accuracy for predicting recovery of wall motion after revascularization in patients with short-term hibernation than does myocardial perfusion imaging. However, the perfusion imaging protocol was not designed to optimize the accuracy of SPECT imaging for detecting ischemia, viability or flow reserve, as sestamibi was injected during low dose, rather than maximal, inotropic stimulation. It is also noteworthy that LDDE in the current study failed to predict recovery of wall motion after revascularization with the same accuracy that has been reported in previous studies of patients with CAD and chronic LV dysfunction (6) and patients with LV dysfunction after myocardial infarction (15,16). Combining the 115 myocardial segments with systolic dysfunction in groups A and B in the study of Barilla et al. (13), LDDE achieved a sensitivity and specificity of only 69% and 60%, respectively, for predicting improved regional wall motion after revascularization, with calculated positive and negative predictive accuracies of only 76% and 51%, respectively. The low specificity (but not the low sensitivity) may be related to the short follow-up time (mean 40 days) after revascularization, as LV function may continue to improve between 5 weeks and 7 months (17).

In addition to the short follow-up period, several other aspects of the study of Barilla et al. limit full interpretation of the results leading to their conclusions. Grading the degree of coronary collateral development by angiography has notorious difficulty and imprecision. The authors considered only well-developed collaterals (grade 3) as evidence of collateral flow. Although this establishes that collateral flow was indeed present in the group defined as showing collaterals, it leaves open the distinct possibility that collaterals were also present, but less well developed, in the majority of the group considered “without” collateral vessels. There clearly was sufficient blood flow through antegrade or collateral channels to maintain tissue viability and presumably to allow for an increase in transmural contractility in response to dobutamine. Second, because heart rate and blood pressure data are not provided, it is unclear whether the increase in myocardial demand with dobutamine was similar between the groups with and without well-established collaterals. Although both groups showed increased contractility as evidence of increased demand, differences in rate–pressure product between the two groups could influence the level of demand and hence the appropriateness of any flow increase. A third issue is the use of sestamibi SPECT imaging to assess regional coronary blood flow reserve. Analysis of sestamibi images provides only relative flow information. In the absence of methods to calculated absolute flow (as can be performed with PET) a flow increase in the hibernating region may go undetected by SPECT imaging if dobutamine produces a similar degree of augmented blood flow to normal regions. It is likely that small increases in blood flow of 10% to 20%, which frequently occur in response to pacing tachycardia or dobutamine (2,5), cannot be detected by SPECT methods, especially when flow is also increasing in normal regions. SPECT also lacks the resolution to determine whether
there is a differential flow response between the endocardium and epicardium in response to dobutamine.

The observations of Barilla et al. provide a basis for further thought and investigation of the coupling and uncoupling of flow and function in myocardium with reversible contractile dysfunction. Prospectively designed studies to evaluate functional and flow responses to inotropic stimulation should provide further insights, but these will require application of quantitative methods to determine absolute blood flow. Although PET can provide such data, the spatial resolution of PET cannot differentiate changes in transmural flow distribution from endocardium to epicardium. To fully address the possibility of uncoupling of flow and function during inotropic stimulation, methods that can evaluate flow-function relationships at the endocardial and epicardial levels, such as contrast echocardiography or contrast magnetic resonance imaging, will be required. The development of such methods should prove to be important investigative tools as new treatments to increase collateral blood flow to ischemic and dysfunctional myocardium, such as laser revascularization and therapies to stimulate angiogenesis, continue to evolve.

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