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Editorial Comment

Response of Dysfunctional Myocardium to Dobutamine

"The Eyes See What the Mind Knows!"*

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In patients with acute myocardial infarction with either successful thrombolytic therapy or percutaneous transluminal coronary angioplasty, the response of the postischemic myocardium to dobutamine is influenced by at least five factors, two of which (extent of viable tissue and degree of residual stenosis) are depicted in Figure 1. For the sake of simplicity, the size of the risk area, the spatial extent and magnitude of collateral blood flow and the effect of beta-blockade are not depicted. If the size of the risk area is small (<12% of the endocardial circumference), function within that area is determined by that of the adjacent myocardium through the tethering effect (1). The amount of collateral blood flow and extent of beta-blockade also modulate the response by causing less myocardial dysfunction for any given dose of dobutamine (2,3).

In the absence of a residual stenosis, the transmural extent of viable tissue within the postischemic myocardium determines the degree of wall thickening for any given dose of dobutamine (Fig. 1, panel A) (4). Low dose dobutamine increases wall thickening only if necrosis is minimal or absent. In the presence of necrosis involving more of the myocardial thickness, systolic thickening starts increasing only at moderate doses of dobutamine, with further increases seen at high doses. If the necrosis is transmural, wall thickening does not increase at any dose. Thus, in the absence of a stenosis, no response at any dose of dobutamine identifies nonviable myocardium.

In addition to the extent of necrosis, the degree of residual stenosis also influences the response of the postischemic myocardium to dobutamine (Fig. 1, panel B) (5). To achieve improvement in wall thickening, myocardial oxygen delivery must increase in proportion to oxygen demand, which, at any given dose of dobutamine, is influenced by the amount of viable tissue. In the absence of a stenosis, blood flow increases in proportion to oxygen demand (6). If a stenosis limits the required increase in blood flow and oxygen delivery, ischemia occurs and wall thickening diminishes despite the presence of viable myocardium. Induction of ischemia in dysfunctional myocardium, therefore, suggests the presence of both viable myocardium and a physiologically significant stenosis.

A perfusion/metabolism mismatch on positron emission tomography implies the presence of rest ischemia (7,8). It is therefore not surprising that it predicts recovery of regional function after revascularization. Because it represents inducible ischemia, a "biphasic response" within a dysfunctional segment on dobutamine echocardiography also predicts recovery in function after revascularization (9). If the necrosis is minimal (Fig. 1 [2 in panel A]) and the stenosis severe (Fig. 1 [d in panel B]), ischemia occurs at a low dose of dobutamine. For the same amount of necrosis, however, ischemia in the presence of a moderate stenosis (Fig. 1 [c in panel B]) occurs only at a higher dose of dobutamine and could be missed if infusion of the drug is terminated at a lower dose. Every attempt should be made to demonstrate the presence of ischemia in a dysfunctional myocardial segment because it may be the best predictor of recovery of function after revascularization.

The lack of demonstration of ischemia, however, does not rule out the presence of viability in the postischemic myocardium. For instance, if the extent of necrosis or the degree of stenosis, or both, is only minimal or absent, then function within the postischemic myocardium will improve incrementally at higher doses of dobutamine. Because blood flow limitation is not the primary cause of the dysfunction at rest, revascularization of such myocardium is unnecessary. Indeed, rest function in this bed will most likely improve spontaneously over several days to weeks and become hypokinetic or normalize (10,11). Because most left ventricular wall thickening at rest occurs because of endocardial thickening, (12,13) a mild reduction in thickening (hypokinesia) indicates that most of the myocardium has escaped necrosis and is hence viable (14). Consequently, in the absence of reduced rest flow, hypokinetic segments need not be evaluated for the presence of viability.

Unlike acute myocardial infarction, the pathophysiology of left ventricular dysfunction in patients with chronic coronary artery disease is poorly understood, mostly due to the paucity of experimental data. One predominant concept is that the decrease in rest function is the result of a stenosis-induced reduction in rest blood flow (15). However, if chronic ischemia were the only cause of this phenomenon, dobutamine infusion would result in further dysfunction. Several studies (16–19), including the one by Chan et al. (19) in this issue of the Journal have demonstrated that improvement in function can be seen in these patients in the presence of dobutamine. These data imply that the amount of flow reserve in the dysfunctional segments in these patients exceeds the degree of functional impairment. It is therefore likely that myocardial function is downregulated compared with rest blood flow (20,21) and may

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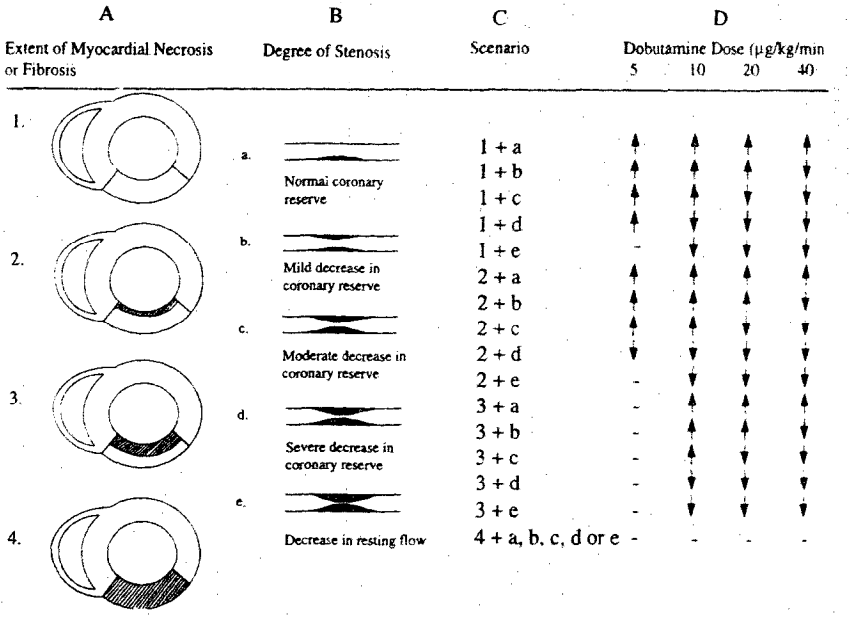

Figure 1. Expected response to different doses of dobutamine after reflow has been achieved in patients with acute myocardial infarction and abnormal function within the infarct zone. **Panel A** depicts the extent of necrosis: 1 = none; 2 = minimal; 3 = moderate; 4 = extensive. **Panel B** illustrates the severity of stenosis whereby the degree of stenosis is defined in terms of its ability to reduce coronary flow reserve: a = normal flow reserve; b = mildly reduced flow reserve; c = moderately reduced flow reserve; d = severely reduced flow reserve; e = reduced rest flow. **Panel C** denotes the possible combination of the extent of necrosis (**panel A**) and degree of stenosis (**panel B**). **Panel D** shows the expected response to dobutamine according to the scenario shown in **panel C**. **Arrows** in the same direction indicate a greater response than that at the previous stage. The responses in chronic coronary artery disease could be different from those depicted here, depending on the extent of myocardial downregulation and collateral perfusion. See text for details. — = no change.

explain why low dose dobutamine improves function in these segments. In this instance, because flow limitation is the cause of reduced myocardial function, revascularization should result in its improvement.

Another emerging concept to explain myocardial dysfunction in chronic coronary artery disease is that of "repetitive stunning" (22). Rest blood flow may be normal in patients with chronic left ventricular dysfunction in regions supplied by either occluded vessels (because of collateral flow) (22,23) or severely stenotic vessels (because of adequate anterograde and collateral flow) (24). These patients, however, have minimal flow reserve, which limits oxygen delivery even during modest physical effort. The resulting oxygen supply/demand mismatch causes ischemia, repetitive episodes of which result in perpetual myocardial "stunning." In such patients, function improves at low doses of dobutamine because of some residual coronary flow reserve, before becoming worse at higher doses (the biphasic response) (9). Revascularization in this setting also results in recovery of function.

One way to unify these two concepts of myocardial dysfunction in chronic coronary artery disease is to take into account the natural history of the disease. When the stenosis is subcritical, rest flow is normal, but repetitive stunning can result in persistent myocardial dysfunction. In this instance, positron emission tomography will show normal rest perfusion (23,24). As the stenosis severity worsens, rest flow will be reduced, and both metabolism and function will be downregulated as a consequence. In this instance, positron emission tomography will show reduced perfusion with intact metabolism (7,8). When blood flow is reduced below levels capable of maintaining cellular viability, necrosis and fibrosis will occur. In this situation, positron emission tomography will demonstrate lack of both flow and metabolism. The mechanism or mechanisms responsible for dysfunction in a particular patient, or even in different myocardial segments within the same patient, are difficult to ascertain without an assessment of myocardial blood flow.

On the basis of the previous discussion, one can see some of the deficiencies in the study by Chan et al. (19), which are not very different from those found in other similar studies. Why was dobutamine stopped at a dose of 10 μg/kg per min in 50% of patients and not in the other 50%? What were the results in patients who continued to receive incremental doses of dobutamine? Why did the authors, like others before them, define only improvement in function during dobutamine as evidence

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for viability? What would their results have looked like if they had also included worsening of function? Admittedly, akinetic segments can show worsening of function simply by changes in load, but it is unlikely that all such segments within a vascular bed will behave similarly. For example, akinetic apical segments are more likely to show dyskinesia with change in load than akinetic segments elsewhere in the left ventricle. Because revascularization is not provided to individual myocardial segments but to an entire vascular territory, it is crucial to evaluate the aggregate behavior of an entire territory rather than just a single segment before proceeding with a revascularization procedure. In the study by Chan et al. (19), the finding that 50% of hypokinetic segments did not show improved function during dobutamine infusion implies that either these segments were supplied by severely stenotic vessels (Fig 1 [? in panel A and d in panel B]) or the dose of dobutamine required to elicit contractile reserve was not achieved. Obviously, therefore, dobutamine echocardiography did not fare as well as positron emission tomography for assessing viability in these segments.

Why were cutoffs used for fluorine-18 fluorodeoxyglucose uptake to define viability? If we ignore the partial volume effect, then the myocardial uptake of this tracer should be roughly proportional to the number of viable cells. Viability within a myocardial segment is a continuum based on the number of nonnecrosed cells rather than an "all or none" phenomenon (25,26). Was flow by positron emission tomography normal in some dysfunctional segments? How did these segments respond to dobutamine? It is also important to point out that viability data on positron emission tomography are usually acquired only at rest. The influence of degree of stenosis on blood flow and metabolism during dobutamine infusion is usually not evaluated using this technique.

Like others before them, Chan et al. (19) state that only recovery in function after revascularization denotes "clinically relevant" viability. Indeed, recovery in rest function after revascularization may not be the only benefit of having nonischemic viable myocardium (21). Rest function improves after revascularization only when most of the endocardium is viable (14). The rest of the myocardium may be viable, but because it does not participate greatly in rest wall thickening (12,13), rest function will not improve after revascularization if the endocardium is necrosed or fibrosed. However, the release of catecholamines during stress could increase thickening in the viable myocardium in the outer layers of the left ventricular wall (4,5) and contribute to enhanced global left ventricular systolic performance during that period. Thus, perhaps a better way to evaluate the success of revascularization is to assess left ventricular systolic function and size during stress rather than at rest. The presence of viable myocardium in the outer myocardial layers may also contribute to maintaining left ventricular shape and size and to preventing infarct expansion and consequent heart failure and late mortality after acute myocardial infarction (10,27,28). Thus, revascularization of dysfunctional myocardium exhibiting evidence of ischemia makes eminent sense even if recovery in rest function is not seen after the procedure.

Most diagnostic tests are interpreted on the basis of specific patterns. Although expedient, "pattern reading" leads to oversimplification in interpretation of test results. A case in point is the "fixed" thallium defect. Even when such a defect has considerable thallium uptake, it is often thought to represent "scar." In fact, thallium uptake in the myocardium several hours after injection, even when reduced, indicates the presence of viable cells, and patients with this pattern, demonstrate functional improvement after revascularization (25,29,30). As would be expected, positron emission tomography reveals intact metabolism in many segments with fixed thallium defects and has thus become the reference standard for assessing viability in such patients (7,8).

The same limitations of pattern reading are true for assessing viability using dobutamine echocardiography. In fact, even the expected responses to dobutamine in the postischemic myocardium illustrated in Figure 1 are an oversimplification. Important confounding variables, such as the extent and magnitude of collateral blood flow, have been omitted for the sake of simplicity. Figure 1 merely attempts to provide a framework within which the results of dobutamine echocardiography can be interpreted. For correct interpretation, however, a comprehensive understanding of coronary pathophysiology and knowledge of the specific clinical scenario are required. After all, as Goethe put it, "The eyes see what the mind knows."

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