Dysfunction in Collateral-Dependent Myocardium
Hibernation or Repetitive Stunning?

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It is now well established that myocardial dysfunction, once thought to be indicative of irreversible tissue damage, is in many cases reversible. This has led to the concepts of myocardial “stunning” and “hibernation.” In both of these conditions, myocardial function is reversibly compromised; in stunning, myocardial function is decreased in response to a previous ischemic insult, and blood flow is normal or near-normal, whereas in hibernation, function is reduced in response to a continuing flow deficit. However, as reviewed in detail recently, in the clinical environment, a sharp distinction between stunning and hibernation may not always be feasible because in a patient with resting flow abnormalities, any increase in demand due to normal daily activities would be expected to lead to ischemia and posts ischemic dysfunction. Thus, stunning may be superimposed on hibernation. In this issue of Circulation, Vanoverschelde et al provide further insight into the mechanisms underlying myocardial dysfunction in coronary artery disease. They studied patients with noninfarcted but dysfunctional collateral-dependent myocardium and found that myocardial blood flow was not decreased significantly in these sectors compared with blood flow in collateral-dependent myocardium with normal function in a second group of patients. Thus, the dysfunctional segments do not fulfill the normal definition of “hibernation,” in which blood flow is chronically reduced. However, in a subset of patients in whom myocardial flow reserve was determined by vasodilation with intravenous dipyridamole, dysfunctional segments had a very limited flow reserve. Normokinetic collateral-dependent segments, however, had a normal flow reserve. The authors concluded that repetitive stunning, rather than a chronic low-flow state of perfusion-contraction coupling, was responsible for the myocardial dysfunction. However, because the dysfunctional segments showed pronounced structural abnormalities, the tissue also differs from normal models of acute “stunning,” in which structural changes are mild.

An important facet of this study was the use of positron emission tomography (PET) with the blood flow tracer N-ammonia to obtain quantitative regional blood flow measurements. A recent study from the same laboratory validated the accuracy of this method for regional blood flow quantification, demonstrating an excellent correlation between PET-measured blood flow and invasive blood flow measurements with radiolabeled microspheres in dogs. This is supported by research from two other laboratories, which also found PET and N-ammonia to give accurate measurements of regional myocardial blood flow.

Histology and Function
A striking finding in tissue biopsies taken from dysfunctional sectors was a significant degree of histological abnormality. The cellular abnormalities found in dysfunctional collateral-dependent myocardium, which included dedifferentiation of myocytes with loss of contractile machinery, imply that a return of function to these segments would be expected to be delayed after intervention to improve myocardial blood flow and flow reserve. Few clinical studies have measured regional function early after revascularization, and results of those that have been performed have been varied. In patients studied by transesophageal echocardiography immediately (within 15 minutes of discontinuation of cardiopulmonary bypass) after coronary artery bypass grafting, 57% of severely dysfunctional segments showed immediate improvement in wall thickening; no further improvement was observed 8 days later. In contrast, in patients undergoing coronary angioplasty, no significant improvement in wall motion was found 3 days after revascularization, but by 67 days after revascularization, wall motion had improved significantly. A third study found recovery of asynergic myocardium to be biphasic, with partial recovery within 15 minutes and further recovery at 13 weeks. These results can be compared with those obtained in conscious dogs in which a partial stenosis was maintained for 5 hours, leading to an approximately 40% decrease in wall thickening. Transmural blood flow in the ischemic area was decreased to approximately 75% of control tissue with normal subepicardial flow but a 50% reduction in subendocardial flow relative to remote tissue. After release of the partial stenosis, reactive hyperemia occurred in the subendocardium, but function did not
improve immediately instead recovering progressively over 7 days. The absence of early functional recovery in this experimental model of nontransmural ischemia emphasizes that care must be taken in extrapolating from in vitro perfused heart models of global ischemia where function may return immediately on normalization of blood flow to in vivo experiments. Although it could be argued that the flow deficit in the study of Matsuzaki et al was too severe to allow "pure" hibernation and concomitant immediate functional recovery, this would imply that pure hibernation in vivo can occur only over a very limited range of flow reduction, even in the absence of changes in demand; in humans, increased demand during activity will introduce another layer of complexity.

Vanoverschelde et al did not measure regional function early after revascularization, but 12 patients with collateral-dependent dysfunction did undergo contrast left ventriculography 5–8 months after revascularization. All patients demonstrated a significant improvement in function at this time. It clearly will be of great interest to learn the time course of functional recovery in patients with this type of structural abnormality.

**Oxygen Consumption and Metabolism**

The collateral-dependent dysfunctional sectors were characterized by near-normal MVO2, increased 18F-fluorodeoxyglucose (FDG) uptake, and elevated tissue levels of glycogen. MVO2 has been demonstrated to be paradoxically high in dyskinetic myocardium during pharmacological dyskinesis with lidocaine—approximately 70% of MVO2 in remote tissue.13 Because in the empty vented state lidocaine decreased MVO2 further, to 27% of that in the contracting state, it was concluded that passive wall stress was a likely explanation for the near-normal MVO2 in segments undergoing systolic bulging. A similar decrease in MVO2, to approximately 70% of remote sectors, was found in reversibly injured canine myocardium within the first 24 hours after a 3-hour coronary artery occlusion.14 The findings of Vanoverschelde et al4 that MVO2 in dysfunctional segments was decreased ~28% relative to remote segments thus are consistent with results obtained in both pharmacological dyskinesis and reversible ischemic injury. This suggests that despite the depletion of contractile material in the dysfunctional collateral-dependent segments, passive stretch increases MVO2 above basal levels in a similar fashion to ultrastructurally normal tissue.

A number of biochemical mechanisms could be responsible for increased FDG uptake in collateral-dependent myocardium. Increased glycolysis has been demonstrated in both acute ischemia and posts ischemic myocardium. In acute ischemia, glucose transport and glycolytic flux are stimulated by changes in regulatory metabolites when the flow deficit is mild, whereas progressive glycolytic inhibition takes place as ischemia becomes more severe and limits clearance of lactate and protons. Increased FDG uptake was found 24 hours and 1 week after reperfusion in reversibly injured canine myocardium following transient coronary artery occlusion16,17 and was shown to reflect increased glycolytic flux 24 hours after reperfusion. Interestingly, increased FDG uptake was not found early (1–4 hours) after reperfusion, in keeping with many experimental findings in acute animal models. Also, elevated glycolytic flux in reperfused relative to remote myocardium was found only when glucose utilization was low in remote tissue, suggesting that glycolysis in stunned myocardium was less susceptible to regulation by humoral factors such as increased plasma fatty acid levels.17

In addition to metabolite-induced changes in glucose metabolism, changes in gene regulation could occur in response to chronic mild or repetitive ischemia, leading to upregulation of enzymes in the glycolytic pathway. Experimental verification of such mechanisms awaits a suitable animal model. Glucose taken up into myocardium also can be incorporated into glycogen, and studies in isolated rat hearts have demonstrated replenishment of glycogen in posts ischemic rat heart.19 In view of the elevated tissue glycogen levels in the collateral-dependent dysfunctional sectors, it would be of value to obtain a better understanding of glycogen homeostasis in this tissue.

Finally, the increasing availability of quantitative information about blood flow and metabolism from PET and other techniques raises the question of how best to use these data to determine, for example, whether blood flow in a given segment is normal or abnormal. Comparison of quantitative blood flow values to a normal data base or to a control patient group may demonstrate that blood flow in a dysfunctional segment is in a normal range but does not necessarily mean that blood flow in that segment is appropriate for the cardiac workload in that patient; demand may be elevated by, for example, an increased rate pressure product or changes in wall stress after ventricular dilation. Thus, caution must be used in making comparisons of quantitative data between groups of patients or between patient groups and normal data bases. In the study of Vanoverschelde et al,4 in view of the extremely limited flow reserve in the group 2 patients with dysfunctional collateral-dependent segments, it is possible that in at least some of the patients flow reserve was exhausted in the dysfunctional segments and that blood flow was insufficient to meet demand in that individual. Thus, a contribution of hibernation as well as repetitive stunning in some patients cannot be ruled out, despite the similarity in mean blood flow in normokinetic and dysfunctional collateral-dependent segments. However, the findings of Vanoverschelde et al4 strongly suggest that demand-induced dysfunction and consequent posts ischemic dysfunction are likely to play an important role in dysfunction in hibernating myocardium and that recovery of dysfunctional segments after revascularization is likely to be delayed frequently by the ultrastructural changes that have occurred.

**References**


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