Resting Blood Flow in Hypocontractile Myocardium
Resolving the Controversy

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The question of whether reductions in blood flow occur under resting conditions in viable nonischemic myocardium in patients with coronary artery disease has been debated for >3 decades. Some early measurements reported reductions in resting left ventricular flow that seemed difficult to attribute to admixture of scar tissue with normally perfused myocardium. Others failed to show differences between apparently normal individuals and coronary patients. Transient defects in resting 201Tl scans observed in the late 1970s supported the concept of relative hypoperfusion of viable nonischemic myocardium. They were usually associated with severe coronary artery disease but normal or only mildly abnormal left ventricular wall motion and often were less pronounced after bypass graft surgery.

After the initial demonstration of myocardial “stunning” in 1975, it was increasingly appreciated that regional contraction often remained depressed after transient ischemia despite restoration of normal flow. Although stunning could persist for several days, its contribution to chronic left ventricular dysfunction remained unsettled. In a 1985 perspective on randomized trials of coronary bypass surgery in chronic stable angina, Rahimtoola proposed the term “hibernating myocardium” to describe a situation in which “contractility and metabolism and ventricular function are reduced to match the reduced blood supply.” He contrasted this situation with stunned myocardium, in which flow was not reduced proportionately to function. In an earlier study, Diamond and colleagues had referred to hypocontractile myocardium showing improved contractile function after coronary bypass surgery as being in “a state of function ‘hibernation’” but did not address whether preoperative blood flow was reduced concomitantly. Some subsequent studies have also used the term “hibernation” without reference to blood flow, whereas others have postulated that reversibly hypocontractile myocardium represents chronic stunning.

Interest in whether resting blood flow is normal or reduced in hypocontractile myocardium has persisted primarily because of the conceptual differences implied, ie, whether perfusion and contractile function are reduced proportionately, thereby maintaining a normal flow-function relationship (hibernation), or whether flow remains at the same level as in normally contracting myocardium, resulting in a flow-function imbalance (stunning). Mechanistically, stunning is regarded as an adverse effect of ischemic injury, whereas hibernation implies a presumably protective adaptation to limited flow and/or ischemic episodes that serves to maintain myocardial viability.

Although rest single-photon emission computed tomography imaging frequently identifies areas within the left ventricle in which full-thickness flow is reduced, the magnitude of flow reduction and possible contribution of scar tissue remain difficult to address quantitatively. However, there is now substantial experience with positron emission tomography to quantify full-thickness myocardial perfusion in humans. Several groups have reported quantitative measurements of resting flow in patients having areas of chronically hypocontractile ventricular tissue. Heusch et al have recently reviewed values from 26 studies in which contractile deficits were reduced or abolished after revascularization or in which preserved uptake of fluoro-2-deoxy-D-glucose in hypocontractile areas was demonstrated. Transmural flow in areas with initially reduced contractile function was systematically less ($P<0.05$) than in regions with normal contractile function in 17 of the 26 reports. The question of whether, and to what degree, reductions were related to scar tissue within hypocontractile areas remained difficult to address.

The study of Selvanayagam et al in the present issue of Circulation provides convincing evidence for the hibernation paradigm. Resting myocardial flow (normalized for rate-pressure product) was measured with first-pass MRI before and 24 hours after percutaneous coronary intervention (PCI) in 27 patients with $\geq 80\%$ stenoses and at least 1 dysfunctional myocardial segment. Segmental function was evaluated with cine MR before and 9 months after revascularization in 25 of the 27 patients. Four findings are of particular interest:

1. Full-thickness flow in segments supplied by stenotic arteries was decreased relative to flow in other segments before PCI ($0.7\pm 0.2$ versus $1.2\pm 0.3$ mL · min$^{-1}$ · g$^{-1}$) but increased to similar values after PCI ($1.2\pm 0.2$ versus $1.3\pm 0.2$ mL · min$^{-1}$ · g$^{-1}$).

2. After PCI, systolic wall thickening increased substantially in originally stenotic segments ($8\pm 17\%$ to $40\pm 19\%$) while not changing appreciably elsewhere.

3. Because the MRI study included delayed enhancement imaging, it was possible to identify areas of scarring.
within hypocontractile segments. Eighty-seven percent of originally dysfunctional segments not showing hyperenhancement improved systolic thickening by at least 15% and/or wall motion scores by at least 1 grade on the follow-up cine MR. Myocardial flow in these segments increased from 0.8±0.2 mL·min⁻¹·g⁻¹ before PCI to 1.2±0.2 mL·min⁻¹·g⁻¹ after PCI, whereas flow in remote myocardium with normal function and no hyperenhancement was unchanged (1.3±0.2 versus 1.4±0.2 mL·min⁻¹·g⁻¹).

As would be expected with an admixture of viable myocardium and scar tissue, hypocontractile segments that did contain hyperenhanced areas showed progressively less increase in full-thickness flow in response to PCI as the extent of hyperenhancement increased. In segments in which hyperenhancement predominated, flow did not change significantly (0.4±0.1 mL·min⁻¹·g⁻¹ before PCI versus 0.3±0.2 mL·min⁻¹·g⁻¹ after PCI).

Because these findings are derived from areas of myocardium supplied by severely stenotic arteries in a modest number of coronary patients, they are not necessarily applicable to less severe disease and other patient groups. However, the present study is distinctive in (1) comparing quantitative measures of flow and function before and after relief of stenosis in individual patients, (2) documenting corresponding improvements in segmental flow and function after revascularization, and (3) eliminating myocardial scarring as a confounding factor in interpreting baseline reductions in flow and function. Although the current quantitative magnetic resonance perfusion technique is relatively new, the magnitude of the average reduction in full-thickness flow in dysfunctional segments not showing hyperenhancement (33%) strengthens the conclusion that the segments were indeed “hibernating” before PCI. Whether the full-thickness flow reductions included substantial transmural variation remains speculative.

A further point of interest is that end-diastolic wall thickness in hibernating segments, which was reduced before PCI (6.5±1.1 mm), increased significantly after PCI (9.3±2.0 mm) despite a lack of change in overall left ventricular mass index (63±11 g/m² before PCI and 61±10 g/m² after PCI) or left ventricular end-diastolic volume index (76±16 and 74±19 mL/m²). In their recent review, Heusch and colleagues summarized the various morphological changes reported in experimental animals and humans in myocardium thought to be hibernating. These include myocyte loss, myofibrillar disintegration and loss within remaining myocytes, increased glycogen deposition, mitochondrial alterations, reductions in sarcoplasmic reticulum and connexin 43, disorganization of cytoskeletal components, and increased interstitial fibrosis. Vanoverschelde et al have reported that the return of segmental function after bypass graft surgery follows a monoexponential time course with a median time constant of 23 days and that the rate of recovery correlates with the proportion of altered cardiomyocytes in biopsies obtained at the time of surgery. Thus, in the present study, the increase in end-diastolic wall thickness accompanying improved systolic contraction at 9 months may involve reversal of morphological changes as well as local hypertrophy.

An additional, incompletely understood consideration is that morphological changes in experimental models of hibernation have been reported in remote nonhibernating tissue as well as in hibernating areas. Although incompletely understood, these global changes appear to be associated with increases in ventricular preload. It remains to be determined whether human myocardium also shows morphological changes in areas remote to hibernating areas.

As complexities of myocardial responses to flow restriction have continued to be identified, shortcomings of the dichotomous characterization of hypocontractile myocardium as hibernating or stunned have become increasingly apparent. The findings of Selvanayagam and colleagues confirm that resting flow is reduced in viable reversibly hypocontractile myocardium in clinically stable coronary patients, with apparent flow-function matching before and after revascularization. Myocardial stunning also occurs periodically in hibernating tissue, however, reflecting the delicate balance of the flow-function relationship, and appears at least sometimes to be involved in generating the hibernating state. A 1987 study indicating that repeated episodes of stunning can lead to hibernation has now been confirmed. It is now also clear that the development of hibernation involves ischemic preconditioning and upregulation of complex gene programs that are just beginning to be identified. Hypertrophic remodeling of arterial microvessels may be an additional consideration. Thus, although reductions in resting flow do occur in reversibly hypocontractile myocardium, debates on hibernation versus stunning are being usefully supplanted by efforts intended to provide additional insight into the various mechanisms underlying the broad spectrum of responses to flow reduction.

Disclosure

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References


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