Repetitive stunning, hibernation, and heart failure: contribution of PET to establishing a link

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THE CLINICAL PROBLEM

Heart failure is common and mortality from heart failure is increasing (49). Thrombolytic therapy has reduced the mortality of myocardial infarction, but many survivors go on to develop heart failure, which is expensive to treat, associated with a poor prognosis (17), and accounts for over 5% of hospital admissions (exceeding those for acute myocardial infarction). Despite advances in medical treatment, prognosis remains poor; the 5-year mortality for established heart failure exceeds that for the majority of cancers (18, 49).

Medical Treatment of Heart Failure

A number of large trials have confirmed that angiotensin-converting enzyme (ACE) inhibitors reduce the mortality of patients with established heart failure. The evidence for the widespread use of ACE inhibitors in patients with heart failure is compelling and both β-blockers and spironolactone further reduce mortality in chronic heart failure (16, 32, 52, 55). Although these advances in the medical therapy of heart failure are significant, it is important to appreciate that the prognosis and quality of life for these patients remain poor. Up to a third of patients gain no symptomatic benefit from ACE inhibitors, and when objective measures of left ventricular function and exercise tolerance have been made in large trials, treatment has resulted in little demonstrable improvement (19, 30, 80).

Postischemic Heart Failure

In over two-thirds of cases, heart failure is secondary to coronary artery disease. The increasingly successful treatment and reduced mortality of acute coronary syndromes has increased the prevalence of chronic heart failure (79). Evidence from nonrandomized studies suggests that in patients with postischemic heart failure, coronary revascularization can lead to symptomatic and prognostic benefits (54). To understand the reasons for the beneficial effects of revascularization, it is necessary to review the underlying mechanisms of heart failure in patients with coronary artery disease. This is generally the result of the following factors.

Permanent myocyte loss due to infarction with scar formation. The size of the infarct can be reduced by prompt thrombolysis with rapid “door to needle” times and primary percutaneous interventions, but a degree of necrosis is usually inevitable, even if clinically silent. The development of a Q wave on the electrocardiogram is generally accepted as confirmatory evidence of a myocardial infarction, but the presence of a Q wave is a poor index of the extent of infarction.

Chronic dysfunction in viable myocardium subtended by stenosed coronary arteries, which recovers after revascularization (hibernating myocardium). This represents the myocardium where the ischemic insult is insufficient to induce necrosis, although the myocardium remains jeopardized, prone to repeated episodes of ischemia, and exhibits markedly reduced contraction. The concept of myocardial hibernation arose from the observation that sustained improvement in left ventricular function may occur after coronary artery bypass grafting (39, 56, 57) and that transient improvement in chronically dysfunctional segments may occur in response to inotropic stimulation (24, 42). Indeed, it has been reported that 40% of left ventricular regions with Q waves or dysfunction following myocardial infarction are not irreversibly damaged (3, 75).

Changes in the remote myocardium (adverse remodeling). The workload of myocardium remote from the site of infarction is increased not only by the loss of contraction in the infarcted zone but also by the jeopardized and dysfunctional myocardium. The changes in ventricular geometry, local wall strain, and filling pressures combine to increase the metabolic requirements of such myocardium that, while “remote” from the site of infarction, adopts a “crucial” role in maintaining cardiac output. These segments undergo compensatory hypertrophy, but in the long-term adverse
“remodeling” and ventricular dilatation occurs leading to heart failure (13, 15, 79).

From the available studies, it is logical to assume that the beneficial effect of coronary revascularization in heart failure derives primarily from recovery of contractile function in hibernating segments which, in turn, may attenuate remodeling (37).

CONTRIBUTION OF PATHOPHYSIOLOGICAL STUDIES

Myocardial Ischemia and Contractile Function

Over 75 years ago Tennant and Wiggers (73) demonstrated that acute ischemia rapidly impairs myocardial contractile function. For many years it was believed that relief of ischemia led to almost immediate normalization of function, provided that necrosis had not occurred. In 1975, Heyndrickx et al. (41) demonstrated, in a conscious dog model, that a 15-min coronary occlusion (a period generally not associated with cell death) followed by reperfusion produced a marked depression in regional contractile function that persisted for at least 6 h after reperfusion. The term “myocardial stunning” was coined to describe this viable tissue that exhibited prolonged postsischemic ventricular dysfunction (7). More recently, stunning has been demonstrated to occur in patients with coronary artery disease after both exercise- and dobutamine-induced ischemia (2, 4).

Several experimental studies have demonstrated that a matched reduction of myocardial blood flow and function, like that hypothesized by Rahimtoola (56, 57), can be maintained for several hours and is generally known as “short-term hibernation,” although many of these studies are limited by the presence of myocardial necrosis (40). More recently, positron emission tomography (PET) studies of myocardial blood flow in humans have provided more impetus to this subject and critical reanalysis of the initial hypothesis. These studies showed that myocardial blood flow in hibernating tissue can vary from normal to slightly reduced (20, 23, 31, 33, 46, 47, 64, 71, 78), while the coronary vasodilator reserve is severely reduced. The reduction of myocardial blood flow demonstrated by some of these studies is much less than that induced in animal models of short-term hibernation (14).

Myocardial Blood Flow in Stunning

In animal models of stunning, the nadir of contractile dysfunction following an episode of myocardial ischemia (generally produced by complete coronary occlusion) is observed despite restoration of normal blood flow (7, 41). Further animal studies demonstrated that stunning could also be induced after exercise in dogs with chronic coronary stenoses (74) and that repetitive episodes of stunning could lead to a longer-term impairment of contractile function (67).

Ambrosio et al. (2) confirmed that exercise-induced ischemia can lead to prolonged postsischemic contractile dysfunction in patients with coronary artery disease despite normalization of the perfusion defects demonstrated by single photon emission tomography (SPET) with $^{99m}$Tc-labeled sestamibi. More recent work from Barnes and colleagues (5) has shown that absolute myocardial blood flow, measured with PET, to postsischemic dysfunctional segments is normal and confirmed the presence of human stunning.

Recently, Rinaldi et al. (60) demonstrated that, as in animals, repetitive episodes of ischemia lead to more profound and persistent postsischemic dysfunction in patients with coronary artery disease and stable exertional angina. The concept that stunning and hibernation may be causally related is supported by a number of more recent experimental studies (26, 27, 45, 48, 50, 68), indicating that flow falls in chronically dysfunctional myocardium after a period of chronic stunning with normal resting flow.

Resting Blood Flow in Patients With Hibernating Myocardium

From the SPET perfusion studies with $^{201}$Tl- or $^{99m}$Tc-labeled sestamibi, hibernating myocardium was initially thought to be due to a matched reduction of resting myocardial blood flow and function distal to a coronary stenosis (56, 57). More recently, a number of studies using PET have demonstrated that transmural blood flow in hibernating myocardial segments is generally within the range of values seen in healthy volunteers with echocardiographically normal left ventricular function (11, 12), whereas a reduction of about 20% can be found in other cases (20, 23, 31, 33, 46, 47, 64, 71, 78).

The measurement of myocardial blood flow by PET has been validated against radioactive microspheres in animals, with comparable results for resting and hyperemic flow in normal human volunteers (11). The literature can on occasion appear confused because variable results have been reported for technical reasons that are beyond the scope of this editorial. In patients with previous myocardial infarction (an almost invariable finding in patients with hibernating myocardium), the presence and amount of scar tissue within a dysfunctional region “dilutes” the flow estimates made with $^{15}$NH$_3$, whereas H$_2$O measures flow per gram of perfusable tissue. This issue has been discussed in more detail previously (13).

Finally, the loss of systolic wall thickening and presence of scarring with wall thinning may result in a 20–25% underestimation of regional radioactivity counts and therefore explain the apparent hypoperfusion of these dysfunctional regions. This is due to the partial volume effect when the ventricular wall thickness approaches the resolution of the camera and can be overcome by appropriate correction, which has unfortunately not been undertaken in all studies. Therefore, direct comparisons of different PET studies that have not considered all the above points may lead to misleading conclusions (14, 40).
Is Impaired Coronary Flow Reserve the Link Between Stunning and Hibernation in Humans?

Coronary flow reserve, which is the ratio of myocardial blood flow during pharmacologically induced hyperemia to baseline flow, decreases as stenosis severity increases and the impairment becomes more severe in those regions with resting myocardial dysfunction (63, 78). Uren et al. (76) demonstrated that in patients with coronary artery disease, flow reserve decreases in proportion to the degree of stenosis severity and is abolished for stenoses above 80% or more of the luminal diameter. Under these circumstances, any increase in cardiac workload above baseline conditions cannot be met by an adequate increase in myocardial blood flow, leading to ischemia. Therefore, in patients with severe coronary artery disease, the limited flow reserve leads to the development of myocardial ischemia, which is often asymptomatic (61), even for small increases of oxygen demand such as those associated with ordinary daily activities (21). Regardless of the blood flow level under baseline conditions, these patients will develop ischemia when oxygen demand is increased (demand ischemia). Thus intermittent episodes of ischemia and consequently postischemic stunning might play a role in the development of chronic reversible left ventricular dysfunction (62, 78). Clearly, under these conditions coronary revascularization would alleviate the chronic ischemic dysfunction by restoring flow reserve. In fact, a unifying feature present in the available studies is the demonstration that a severe reduction in coronary flow reserve is present in chronically dysfunctional myocardium, and recovery of function is believed to be associated with restoration of the flow reserve (Fig. 1).

In summary, there is now considerable evidence that the original concept that prolonged reduction in resting myocardial blood flow is solely responsible for the chronic contractile dysfunction of hibernation (56, 57) is not the predominant finding in humans with chronic posts ischemic ventricular dysfunction. The idea that stunning and hibernation may be causally related by the constraint in flow reserve is supported by a number of recent experimental studies (27, 45, 48, 50, 68). These animal studies indicate that flow beyond a stenosed coronary artery subtending a region of chronic dysfunction falls after a period of chronic stunning. In addition, it is likely that these repeated episodes of intermittent ischemia and reperfusion may lead to sustained changes in the function of the coronary microcirculation (6). This hypothesis is strengthened by the finding that ventricular function improves gradually over some months after bypass surgery and in parallel with the recovery of coronary vasodilator reserve (CVR) (53, 69). There are no studies of the natural history of either resting myocardial blood flow or CVR in patients with coronary artery disease and either normal or dysfunctional myocardium. An observational study of the change in CVR in a cohort of patients awaiting surgical revascularization is currently ongoing, and a randomized controlled trial comparing the strategies of optimal medical treatment with revascularization to optimal medical treatment alone is about to start in the United Kingdom.

**Myocardial Metabolism in Stunning**

In dogs, stunned myocardium is characterized by abnormalities in high-energy phosphate metabolism. After an episode of transient ischemia, which does not induce myocardial necrosis, there is a significant reduction in ATP, and on reperfusion, ATP levels return to normal very slowly (22, 59). In the pig, however, both ATP and creatine phosphate in stunned myocardium do not differ from control tissue (48).

Myocardial glucose uptake in stunned myocardium is increased (38). This increase may be due to increased translocation of GLUT4 transporter to the sarcolemma (51) and is consistent with the previous finding (using PET) of increased myocardial uptake of \(^{18}\)F- fluorodeoxyglucose (FDG) during recovery from exercise-induced ischemia in patients with stable angina (9). The latter is a setting in which myocardial stunning is likely to have occurred (2), and the increased glucose uptake may be required to replenish myocardial glycogen stores that were depleted during ischemia. Furthermore, in the isolated rabbit heart, it has been shown that glycolysis is also enhanced in postischemic myocardium, and functional recovery requires glycolysis during early reperfusion (43). Similar results have been obtained in anesthetized pigs (28) in which FDG uptake in stunned myocardium was variably increased compared with control regions with no consistent transmural differences. Subgroup analysis demonstrated that the variability in the uptake of FDG was related to circulating insulin.
Regional myocardial oxygen consumption has been measured in a canine model of stunning (44). Conscious dogs were subjected to three sequential 10-min coronary occlusions interspersed with 30-min periods of reperfusion. One hour after the last coronary occlusion, segment shortening was reduced by ~40% compared with baseline, whereas myocardial blood flow did not differ from baseline. Simultaneous measurement of myocardial oxygen consumption in the stunned region showed that oxygen consumption did not change compared with baseline.

**Myocardial Metabolism in Hibernating Myocardium**

Semiquantitative assessment of glucose utilization during fasting conditions using FDG and PET has shown an increased FDG signal in chronically dysfunctional segments relative to remote myocardium (72). These data have been confirmed by quantitative measurements of myocardial FDG uptake (25, 31). However, it must be noted that the measurement of fasting FDG uptake is affected by a high degree of intra- and interindividual variability. This might be partly ascribed to physiological inter- and intrasubject differences, but it also derives from the poor counting statistics due to the low uptake of tracer by the myocardium in the fasting condition (10). In normal subjects studied after overnight fasting, myocardial FDG uptake is extremely low (~1–2 \( \mu \text{mol} \cdot 100 \, \text{g}^{-1} \cdot \text{min}^{-1} \)) due to the prevailing lipid utilization (10). In the study of Maki et al. (46), FDG uptake was greater than in normal subjects not only in dysfunctional myocardium, but also in remote myocardium (15 ± 10 vs. 11 ± 10 \( \mu \text{mol} \cdot 100 \, \text{g}^{-1} \cdot \text{min}^{-1} \), \( P < 0.05 \) dysfunctional vs. remote). Similar findings (27) have been reported in pigs instrumented with a proximal stenosis on the left anterior descending coronary artery, which developed chronic dysfunction in the anterior wall of the left ventricle. The uptake of FDG was increased almost twofold in the anterior wall compared with the rest of the ventricle. In addition, ex vivo counting of FDG revealed a transmural gradient of uptake in the dysfunctional segments with higher FDG uptake in subendocardial myocardium.

To overcome some of the limitations due to the fasting condition, the hyperinsulinemic euglycemic clamp has been widely employed during PET with FDG (47). The clamp consists of a combined intravenous infusion of insulin and glucose to achieve a state of physiological hyperinsulinemia while maintaining plasma glucose at normal levels. During the steady state of the clamp, stable metabolic conditions are achieved, which induce the myocardium to switch from free fatty acid to glucose as the main substrate for energy production. During the clamp, segments with chronic contractile dysfunction respond to insulin stimulation by increasing glucose uptake (46, 47), albeit less than remote myocardium (47). Using simultaneous arterial and great cardiac vein sampling in patients undergoing bypass surgery, Ferrari et al. (29) reported that hibernating myocardium exhibits net lactate extraction. Although net transmural extraction does not rule out subendocardial lactate production and ischemia (36), increased...
glucose utilization in hibernating myocardium does not seem to represent increased anaerobic metabolism, as seen during ischemia (10), but might be secondary to an increased expression of the GLUT-1 glucose transporter (8, 70).

Oxygen consumption in chronically dysfunctional but viable myocardium has been assessed using \([1^1]C\) acetate and PET in a number of different studies (34, 35, 65, 77, 78). In three studies (34, 35, 77), acetate washout \((k)\) in hibernating tissue was found to be reduced compared with remote myocardium. However, for example, if one considers the \(k\) values in the paper by Vanoverschelde et al. (78) rather than the percent changes between regions, it is clear that in patients with occlusion of the left anterior descending coronary artery, but without anterior wall dysfunction (group 1), the \(k\) values in remote and collateral-dependent myocardium were comparable \((0.058 \pm 0.008 \text{ vs. } 0.054 \pm 0.010 \text{ min}^{-1}; P = \text{not significant})\), whereas in patients with occlusion and dysfunction (group 2), the \(k\) values in remote and collateral-dependent myocardium were different mainly due to a higher \(k\) in remote myocardium \((0.068 \pm 0.02 \text{ vs. } 0.049 \pm 0.015 \text{ min}^{-1}; P < 0.001)\). In fact \(k\) in the remote myocardium of group 2 patients was also significantly higher than the \(k\) value in remote myocardium of group 1. The same applies to the study of Gropler et al. (35) in which the \(k\) value in remote tissue \((0.065 \pm 0.02 \text{ min}^{-1})\) was higher than in hibernating tissue \((0.048 \pm 0.018 \text{ min}^{-1}; P < 0.001 \text{ vs. remote})\). In addition, in the same study \((35)\) \(k\) in remote and previously hibernating myocardium measured after successful revascularization were comparable \((0.055 \pm 0.008 \text{ vs. } 0.055 \pm 0.011 \text{ min}^{-1}; P = \text{not significant})\) and, in absolute terms, were lower than the \(k\) value measured in remote tissue before revascularization. This seems to parallel the regional differences in blood flow between remote and hibernating segments discussed earlier and suggests that these differences are due, at least in part, to increased workload and oxygen consumption in remote segments. Finally, in the second paper by Gropler et al. (34), hibernating and remote segments had similar \(k\) values \((0.061 \pm 0.014 \text{ vs. } 0.064 \pm 0.015 \text{ min}^{-1}; P = \text{not significant})\).

**BACK TO CLINICAL**

The concept of hibernation was derived from clinical observations. Almost 30 years ago clinicians and surgeons observed that chronic myocardial dysfunction, present before coronary bypass, often improved following revascularization (1, 58). In 1974, Gorlin’s group (42) showed that the asynchronous left ventricle could improve its function transiently during catecholamine stress (“The epinephrine ventriculogram”). All this led Diamond et al. (24) to write in 1978 that “ischemic noninfarcted myocardium can exist in a state of function hibernation” in an experimental dog study with acute ischemia. Rahimtoola (56, 57) expanded and increased the awareness of this concept and noted “there is a prolonged subacute or chronic stage of myocardial ischemia that is frequently not accompa-

ned by pain and in which myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply.”

The relationship among myocardial stunning, hibernation, and heart failure remains complex. Some patients with coronary disease do not stun, others suffer repeated, but clinically silent episodes of stunning after normal daily activities, and if such episodes are frequent with incomplete recovery of contractile function before the next insult, chronic ventricular dysfunction may ensue. Such repetitive stunning may trigger the development of myocardial hibernation, but it is important to appreciate that the latter is associated with a number of changes in myocyte metabolism and structure (13). As discussed above, we propose that in patients such changes in the myocyte are dependent on the time that the blood supply to such myocardium remains jeopardized and subject to demand ischemia. Tissue may progress from a phase of “functional hibernation” (not associated with significant changes in the contractile protein apparatus and with rapid functional recovery following revascularization) to a phase of “structural hibernation” with evident ultrastructural abnormalities within the myocyte. In the latter case scenario, functional recovery after revascularization is more prolonged and dependent on de novo protein synthesis and a period of myocyte repair. By contrast, if this condition of deranged blood supply persists, myocytes will eventually die through necrosis and/or apoptosis (Fig. 2), which demonstrates that hibernating myocardium is not adapted to chronic underperfusion and ischemia (25). The cellular degeneration and myocyte loss together with reparative fibrosis combine to deteriorate the structural and functional integrity of the left ventricle which, if advanced, will at best only be partially reversible after revascularization. It therefore seems appropriate to offer these patients revascularization early in the natural history before “structural hibernation” occurs (25, 66).

There is no doubt that the pathophysiology of hibernation and its potential links with stunning are only partially understood. However, clinically there is now wide consensus on the importance of identifying and treating hibernating myocardium in patients with coronary artery disease and heart failure. Although proper ad hoc randomized studies are needed before a definitive influence on clinical practice is achieved, the contribution of the existing experimental studies is compelling and, if necessary, proves once more that no real progress is possible in medicine without the foundations of proper basic and clinical research.

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