Pathophysiology of myocardial hibernation. Implications for the use of dobutamine echocardiography to identify myocardial viability

Jean-Louis J Vanoverschelde, Agnès Pasquet, Bernhard Gerber, Jacques A Melin

Since the pioneering works of Tennant and Wiggers, it has been known that total ischaemia leads to a prompt cessation of contraction and eventually results in the appearance of cell damage and irreversible myocardial necrosis. Accordingly, in the minds of many cardiologists, the discovery of an abnormal regional contraction in a patient with coronary artery disease had long been equated with the presence of irreversible myocardial necrosis. However, with the advent of recanalisation treatment, evidence progressively accumulated that prolonged regional “ischaemic” dysfunction did not always arise from irreversible tissue damage and, to some extent, could be reversed by the restoration of blood flow. These observations have led to the speculation that chronically jeopardised myocardium, which is often referred to as “hibernating”, could spontaneously downgrade its contractile function and minimise its energy requirements to prevent the appearance of irreversible tissue damage. During the past decade, the pathophysiology of the hibernating myocardium has received considerable attention and has fostered the development of several new modalities aimed at predicting the return of left ventricular function after revascularisation. Among these modalities, dobutamine stress echocardiography has recently emerged as a safe, non-invasive, and accurate way of identifying viable myocardium. It is the purpose of this paper to review some of the more recent advances in the understanding of the pathophysiology of chronic myocardial hibernation and the use of dobutamine echocardiography to identify viable myocardium. Emphasis will be placed on regional perfusion–contraction matching in both the experimental and the clinical setting, on the peculiar morphological changes that have been shown to occur in the hibernating myocardium, on the determinants of mechanical reversibility after restoration of adequate coronary patency, and on the presence of recruitable inotropic reserve.

Perfusion–contraction matching in myocardial hibernation

EXPERIMENTAL DATA
The tight coupling between coronary flow, myocardial oxygen consumption, and contractile performance of the heart is a fundamental principle of cardiac physiology. Because of the small extraction reserve of oxygen, decreases in coronary blood flow rapidly translate into decreases in contractile performance. Work from Gallagher and colleagues and Vatner has demonstrated the existence of a close coupling between regional myocardial blood flow and contraction during graded coronary stenosis. The proportional decrease in regional myocardial flow and function in this setting has been termed “acute perfusion–contraction matching” and is typical of acute myocardial ischaemia. Reperfusion after very short periods of low coronary flow (less than 10 minutes) usually results in rapid and complete restoration of cardiac performance. There is no necrosis, and myocardial ultrastructure is normal. More prolonged periods of coronary flow reduction, up to 15–20 minutes, do not usually cause tissue necrosis but, with reperfusion, are associated with a prolonged, albeit reversible, dysfunction, which has been termed myocardial stunning. Thus, in terms of the flow–function relation, the stunned myocardium is characterised by a state of “perfusion–contraction mismatch”.

The observation that, under acute conditions, myocardial contraction decreases to a level matched to the available blood supply has prompted several investigators to examine whether sustained perfusion–contraction matching could be achieved without inducing necrosis. Several studies in open chest anaesthetised animals undergoing partial coronary occlusion have shown that the heart can indeed adapt to a sustained reduction of myocardiold blood flow and develop a state of sustained “low flow perfusion–contraction matching”, also called short term hibernation. Unlike chronic hibernation, short term hibernation is a fairly fragile and unstable condition. Indeed, superimposition of chronotropic or inotropic stress invariably results in increased lactate production, decreased phosphocreatine, and eventually myocardial necrosis. Over the long term, it is also associated with apoptotic myocyte death, which considerably reduces the number of remaining viable myocytes across the dysfunctional wall.

Although the above findings suggest that a precarious steady state between reduced oxygen supply and decreased oxygen demand can

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be achieved and maintained for some time under particular experimental conditions, they also indicate that such a perfusion–contraction matching is unlikely to persist for weeks or months in chronically affected animals. Accordingly, several groups of investigators have tried to develop experimental models of chronic dysfunction that more closely mimic human myocardial hibernation. Earlier investigators who succeeded in reproducing chronic (1–24 weeks) but reversible regional left ventricular ischaemic dysfunction always ended up with models in which the resting endocardial blood flow was either normal or only marginally decreased. Based on these surprising results, these authors logically postulated that myocardial stunning, whether repeated or chronic, was the most likely explanation for their observations. The fact that, in some of these experiments, the onset of dysfunction was preceded by repeated episodes of acute demand induced ischaemia, and that the severity of dysfunction was directly correlated with the reduction in subendocardial flow reserve, but was unrelated to resting subendocardial blood flow, lent considerable support to this hypothesis. Recent work by Fallavolita and colleagues and Bin and colleagues has nonetheless challenged this point of view. Studying the time course of segmental blood flow in chronically dysfunctional myocardium, these authors found that some of the dysfunctional segments that appeared to be “repetedly stunned” on early examination eventually became underperfused. Interestingly, these segments conserved some degree of flow reserve, suggesting that their reduced myocardial blood flow was somehow secondary to the reduction in resting contractile function, and could serve as a way to increase residual myocardial perfusion reserve. Altogether, the experimental data suggest that myocardial hibernation is a complex, progressive, and dynamic phenomenon that is initiated by repeated episodes of ischaemia, and in which resting perfusion, although initially preserved, may subsequently become reduced, probably in response to the decrease in myocyte energy demand.

HUMAN STUDIES

In general, the above experimental results had been predicted on the basis of human studies in which myocardial blood flow was measured by the use of positron emission tomography (PET). These studies showed that 50–60% of the chronically, albeit reversibly, dysfunctional segments had normal levels of myocardial blood flow, together with severe reductions in flow reserve. In the remaining 40–50% of the segments, myocardial blood flow was reduced. Although on the basis of these studies, one could conclude that approximately half of the dysfunctional segments are mildly underperfused, two important aspects must be considered. First, the level of flow reduction in most studies is not sufficient to justify ischaemic dysfunction. Second, many, if not all the above studies have included a variable proportion of patients with previous myocardial infarction, which greatly complicates the interpretation of the flow data. Flow estimates with PET are crucially dependent on the mass of tissue that actively participates in tracer exchange within the region of interest. In the presence of great spatial tissue heterogeneity, such as occurs in previously infarcted myocardium, flow estimates represent the transmural average between several values, from very low in microinfarcted areas to almost normal in the non-infarcted epicardial zones. Thus, they might not reflect the actual level of flow found in the viable part of the wall. However, based on the animal data, it is fair to postulate that some of these dysfunctional segments must be truly underperfused.

Recruitable inotropic reserve

EXPERIMENTAL DATA

Despite severe resting dysfunction, reversibly injured myocardium might retain the ability to improve function temporarily upon stimulation with catecholamines or calcium, whereas infarcted myocardium does not. The ability of acutely stunned myocardium to improve function upon inotropic stimulation has been known for several years. More recently, short term hibernating myocardium has also been shown to display recruitable inotropic reserve upon stimulation with catecholamines. Schulz and colleagues studied the impact of prolonged dobutamine (a synthetic catecholamine) infusion on regional mechanical and metabolic function in open chest anaesthetised swine undergoing partial occlusion of the left anterior descending coronary artery. During occlusion, dobutamine infusion resulted in a transient improvement of regional mechanical function, which was rapidly followed by further functional deterioration, increased lactate production, decreased phosphocreatine concentrations, and eventually myocardial necrosis. Chen and colleagues also studied the effects of incremental doses of dobutamine (from 2.5 to 25 µg/kg/min) on regional mechanical function in pigs with short term hibernation. They showed sustained improvements in mechanical function at dobutamine doses of 2.5 to 10 µg/kg/min (mean, 4.5; SD, 2.2), but deterioration with higher doses. Similar findings were also reported by Sklenar and colleagues and by Mertes et al. More recently, Gerber and colleagues examined the contractile response to low dose dobutamine (mean, 2.5 µg/kg/min; SD, 1.0) of chronically (six months) dysfunctional non-infarcted, collateral dependent canine myocardium. They also found that dobutamine infusion resulted in improved mechanical function, which persisted for at least 30 minutes. Interestingly, the changes in mechanical function during the application of dobutamine in this study were always accompanied by similar directional changes in myocardial blood flow and oxygen consumption, thus suggesting that some degree of residual flow reserve is needed for the improvement in function to occur.
Pathophysiology of myocardial hibernation

In humans too the hibernating myocardium is capable of improving function when challenged by an inotropic stimulus. Earlier investigators attempting to predict the reversibility of left ventricular ischaemic dysfunction after revascularisation on the basis of inotropic reserve used the response of global ejection fraction to an inotropic stimulus (adrenaline (epinephrine) or postextrasystolic potentiation) at the time of cardiac catheterisation as an index of myocardial viability. Nesto and colleagues were among the first to use this approach. They showed that patients with an ejection fraction < 35% who had a > 10% increase in ejection fraction during inotropic stimulation improved global left ventricular function after revascularisation. More recently, investigators have shown that dobutamine echocardiography could also be used to evaluate the inotropic reserve of chronically hibernating segments. Although these studies largely confirmed that dobutamine echocardiography allows accurate identification of viable myocardium, they also showed that not every segment with hibernating myocardium improves functionally with dobutamine. In a recent study, Gerber et al showed that approximately 25% of the hibernating segments showed no response at all to dobutamine stimulation. In a subsequent study, Gerber et al showed that viable segments without recruitable inotropic reserve had a lower resting myocardial blood flow and a higher 18F-2-deoxyglucose uptake under fasting conditions compared with normal segments or viable segments with recruitable inotropic reserve, a finding that is consistent with either ongoing or impending myocardial ischaemia, and thus with a severely blunted myocardial flow reserve. This hypothesis is supported by the results of studies in which myocardial blood flow was measured at rest and during infusion of a low dose of dobutamine. These studies clearly indicated that improvements in mechanical function during infusion of dobutamine are always accompanied by similar directional changes in myocardial blood flow and oxygen consumption. Taken together, the human data also suggest that sufficient residual flow reserve is needed for a positive inotropic response during dobutamine echocardiography. However, this does not rule out the possibility that some additional factors, such as the presence of structural cardiomyocyte alterations (see below), could also contribute.

Structural alterations in the hibernating myocardium

In addition to the above changes in resting myocardial blood flow and flow reserve, chronic myocardial hibernation is also associated with structural alterations that affect both the cardiomyocytes and the extracellular matrix. Most of the available information on these structural changes has been gathered from studies in which human myocardial biopsy specimens were harvested at the time of bypass surgery. One striking feature of the changes seen in cardiomyocytes is the loss of contractile material. In some cells, this is limited to the vicinity of the nucleus, whereas in others it is very extended, leaving only a few (or no) sarcomeres at the cell periphery. Characteristically, the space previously occupied by the myofilaments is filled with an amorphous, strongly periodic acid Schiff positive material, typical of glycogen. Other organelles are also affected. Mitochondria are small and scattered throughout the myolytic cytoplasm. Nuclei are tortuous, and show uniformly dispersed heterochromatin. Sarcoplasmic reticulum is virtually absent, as are T tubules. From a biochemical point of view, tissue concentrations of ATP, total adenine nucleotides, and phosphocreatine usually remain nearly normal, and mitochondrial function, as reflected by the ADP/ATP and phosphocreatine/ATP ratios, also remains nearly intact, a finding consistent with the observation that oxygen consumption, measured with 13C-acetate and PET, is well preserved in the hibernating myocardium.

Given their severity, the structural changes that affect the hibernating myocardium are likely to affect its ability to respond to an inotropic stimulus and the speed at which it may or may not recover after revascularisation. In recent studies, we have investigated the issue of the time course of functional recovery after revascularisation in a series of patients with chronic left ventricular ischaemic dysfunction, who had undergone surgical revascularisation. In an initial study, we evaluated the extent to which the structural abnormalities contributed to the degree of mechanical recovery after revascularisation. Our results indicated that myocardium that improves function after surgery shows significantly less transmural and subendocardial tissue fibrosis and contains significantly more metabolically active cardiomyocytes than myocardium with persistent postoperative dysfunction. The threshold amount of tissue fibrosis that best differentiates myocardium with postoperative functional improvement from that without such improvement appears to be around 35%. More recently, we also looked at the impact of the structural alterations on the time course of recovery after revascularisation and found that the reversal of left ventricular dysfunction is a slow and progressive phenomenon, which follows a monoexponential time course, with a time constant of 23 days. Intriguingly, the rate of functional recovery in individual patients was quite variable and appeared to be linked to the severity of cardiomyocyte alteration and remodelling. When dysfunctional myocardium displayed little or no structural alterations, considerable recovery could be noted as early as 10 days after revascularisation and complete recovery was usually achieved within the first two months. In contrast, when the structural changes were severe and extensive, the recovery of regional contraction was usually quite delayed and the extent of recovery at six months remained incomplete. These findings suggest that the structural abnormalities seen in the hibernating myocardium directly contribute to mechanical dysfunction and are responsible for the delayed return of contractile function after revascularisation.
performance after revascularisation. These observations have important implications for the design of studies aimed at assessing myocardial viability, because the accuracy of such studies will depend on the duration of the follow up period. Preliminary data also suggest that the severity of the structural changes affecting cardiomyocytes does affect the ability of viable myocardium to respond to dobutamine. In a recent study, Pagano et al showed that the likelihood of a positive inotropic response to dobutamine was inversely proportional to the mass of residual myocytes with severe myofibrillar loss.79

Use of dobutamine echocardiography to differentiate between reversible and irreversible regional dysfunction

The diverging contractile response in dysfunctional but viable and infarcted myocardium in both the experimental and the clinical setting provides the basis for distinguishing between reversible and irreversible tissue injury in patients with coronary artery disease and left ventricular ischaemic dysfunction. Recent advances in non-invasive functional imaging, particularly in digitised echocardiography, and the use of standardised dobutamine infusion protocols, has allowed the application of these concepts on a large scale to patients with left ventricular dysfunction.

Dobutamine echocardiography can be used both in the early postinfarction setting and in chronic left ventricular ischaemic dysfunction. Table 1 summarises its diagnostic accuracy for chronic left ventricular ischaemic dysfunction. Overall, low dose dobutamine echocardiography can predict the reversibility of myocardial dysfunction with a sensitivity of 84%, and a specificity of 81%. During dobutamine infusion, the dysfunctional myocardium may exhibit one of four responses:15:

- A biphasic response, improvement at low dose with deterioration at high dose in 18%, a biphasic response (improvement at low dose with deterioration at high dose) in 18%, a biphasic response (improvement at low dose with deterioration at high dose) in 18%, and no contractile response in 39%. In segments with a biphasic response, improvement usually occurs during the 10 µg/kg/min dose, with the greatest prevalence at 7.5 µg/kg/min. Because the number of segments with deterioration increases in a dose dependent manner, starting at 7.5 µg/kg/min, it is recommended that both the 5 and 10 µg/kg/min stages be recorded and analysed to avoid missing a transitory improvement in wall motion, followed by rapid deterioration. It is noteworthy that the specificity of the test is usually less in hypokinetic segments.80 81 In our hands, only 68% of initially hypokinetic segments with persistent postoperative dysfunction are correctly identified by the low dose dobutamine test. There are several potential reasons for the poor specificity of the dobutamine test in hypokinetic segments. Segmental hypokinesis might reflect the presence of a subendocardial scar and be unaffected by revascularisation. However, if enough non-infarcted myocardium remains in midmyocardial and epicardial layers, such segments could still show improvement with dobutamine.

Tethering by adjacent akinetic segments could also be an explanation. In this case, the segmental response to revascularisation will largely depend on the recovery of the adjacent segments, whereas that to dobutamine will also reflect the changes in segmental contractility, cavity size, and afterload.

Dobutamine echocardiography also permits accurate prediction of the improvement in global ejection fraction after revascularisation. Recently, we studied 73 patients with severe left ventricular dysfunction before revascularisation.18 Of these, a total of 43 improved their left ventricular ejection fraction by > 5% postoperatively. Before surgery, these patients had a greater mean (SD) improvement of wall motion with dobutamine echocardiography (6 (3) v 1 (4) grades; p < 0.001) than those with persistent postoperative dysfunction. Using an improved wall motion > 3.5 grades, dobutamine echocardiography correctly identified 88% of the patients with and 77% of those without functional recovery (accuracy 84%).

Preliminary data from our laboratory also suggest that dobutamine echocardiography might be useful for predicting changes in heart failure symptoms after revascularisation, at
least in the subgroup of patients with no or only minimal functional limitation before surgery.\(^4\)

In these patients, dobutamine echocardiography seems to identify those who will experience symptomatic deterioration during follow up, probably because of continuing left ventricular dilatation and remodelling. In contrast, dobutamine echocardiography seems to be of little use in the subgroup of patients with severe functional impairment—that is, those in New York Heart Association functional classes III–IV. In these patients, bypass surgery always seems to provide symptomatic relief, irrespective of myocardial viability. It appears that the degree of symptomatic improvement is greater in the presence of myocardial viability, a finding that is consistent with previous observations by Di Carli \textit{et al} who used PET to detect the presence of jeopardised myocardium.\(^8\)

Finally, dobutamine echocardiography has emerged as a useful technique for predicting prognosis in patients with chronic left ventricular dysfunction. Several studies have now shown that long term survival is significantly better among patients with echocardiographic evidence of myocardial viability who had been revascularised than in those with either viable myocardium treated medically, non-viable myocardium undergoing revascularisation, or non-viable myocardium treated medically.\(^9\)–\(^10\)

These data support the use of dobutamine echocardiography for the assessment of myocardial viability, because this technique not only allows accurate identification of which patient will improve regional and global left ventricular function after coronary revascularisation, but might also indicate those most likely to benefit with respect to prognosis.

\section*{Ultrasound Tissue Characterisation}

Ultrasound tissue characterisation is a novel approach to defining the physical state of the myocardium that complements assessment of left ventricular function and chamber dimensions with two dimensional echocardiography.\(^11\)–\(^12\) The baseline assumption underlying ultrasound tissue characterisation is that pathological changes affecting the myocardium, including ischaemia, result in alterations of its fundamental physical properties that can be detected using ultrasonic integrated backscatter imaging. Experimental studies have indicated that physiological myocardial contraction and relaxation are paralleled by a cardiac cycle dependent variation of integrated backscatter that reflects regional, intramural contractile performance.\(^13\)–\(^15\) Cyclic variations of the backscatter signal are blunted during experimental myocardial ischaemia,\(^16\)–\(^18\) and recover more quickly than does systolic wall thickening with reperfusion.\(^19\)–\(^21\)

Studies in humans with reperfused myocardial infarction have shown that the assessment of cardiac cycle dependent variations of integrated backscatter allowed accurate delineation of reversible (stunning) from irreversible (infarction) tissue injury,\(^22\)–\(^24\) thus providing a potentially useful adjunct for the non-invasive evaluation of regional contractile function and for the detection of potentially salvageable myocardium.

We have recently studied a small group of patients with chronic coronary artery disease and depressed left ventricular ejection fraction using this approach.\(^25\) To obtain a detailed description of the backscatter features of chronically dysfunctional myocardium, we compared the resting cardiac cycle dependent variations of integrated backscatter measured in these segments with their contractile response to the infusion of low doses of dobutamine. Our results showed that the magnitude of residual cardiac cycle dependent variations of integrated backscatter correlated with the improvement in systolic thickening induced by the infusion of low doses of dobutamine, thus suggesting that the magnitude of cardiac cycle dependent variations of integrated backscatter measured in chronically dysfunctional segments could be a useful adjunct for the non-invasive detection of potentially salvageable myocardium. The mechanisms underlying the maintenance of cardiac cycle dependent variations of integrated backscatter in dysfunctional segments with contractile reserve remain uncertain, however. It has been proposed that the presence of cyclic variations in segments with contractile reserve as opposed to those without contractile reserve is a manifestation of their better nutritive perfusion. This possibility is unlikely, however, in view of the results of the PET studies mentioned above. Moreover, cyclic variations can be measured in isolated superfused contracting muscle in the absence of perfusion and augmentation of myocardial blood flow over baseline levels does not usually influence the magnitude of cyclic variations. Alternatively, maintenance of cardiac cycle dependent variations of integrated backscatter in the absence of overt systolic wall thickening could indicate that some dysfunctional segments contract isometrically against an excessive afterload. Regional afterload mismatch in these segments could result from a primary, albeit reversible, decrease in contractility (for instance as a result of a decrease in myofilament responsiveness to calcium), from the selective damage of the subendocardial layers (because of subendocardial infarction), or from a combination of these two possibilities. Our findings that dysfunctional segments exhibiting cyclic variations also display recruitable inotropic reserve when challenged by dobutamine support the contention that excessive afterload constrains their shortening and that these segments contract isometrically. These data suggest that ultrasonic tissue characterisation provides a measure of intramural contractile function that is relatively independent of resting wall motion or thickening and which parallels contractile reserve.

\section*{Conclusions}

The recent refinements in myocardial perfusion imaging and the results of morphological studies of biopsy specimens from human hibernating myocardium have shed new light on our understanding of chronic myocardial...
hibernation. The pathophysiology of this peculiar condition now appears to be much more complex than previously anticipated. It probably involves a combination of repetitive post-ischaemic dysfunction, which is perpetuated by renewed episodes of ischaemia, and ischaemia–reperfusion induced changes in cell phenotype, which eventually culminate in the dramatic morphological alterations that have been described. These characteristics have a profound impact on our ability to differentiate prospectively between potentially reversible and irreversible dysfunction by the use of dobutamine echocardiography.

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