



# Metabolic imaging: toy or tool?

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Historically the origin of metabolic imaging dates back to the mid-1960s when Evans et al.<sup>1</sup> observed that the ventricular myocardium can be visualized by scintigraphy after intravenous injection of the fatty acid oleate labeled with iodine-131. However, the breakthrough in metabolic imaging was related to the advent of positron emission tomography (PET) in the 1970s. The availability of positron-emitting radionuclides such as carbon-11 opened the possibility of labeling metabolic substrates without altering their metabolic behavior.

Visualization of metabolism allowed insight to be gained into the cellular and molecular mechanisms that establish the link between myocardial perfusion and contractile function.

Although this exciting tool contributed significantly to the understanding of the metabolic response of the myocardium to ischemia<sup>2</sup> and other conditions, metabolic imaging still awaits widespread application in clinical cardiology. This is largely due to the expenses involved in the logistics of PET, which for optimal exploitation requires an in-hospital or near-hospital cyclotron. In view of the increasing costs of health care, it seems legitimate that hospital administrators and politicians continue to ask: Is PET worth the price? Are there less expensive alternate methods which provide the same information for clinical decision making?

This issue of *Heart and Metabolism* provides a critical analysis of the current status of metabolic imaging, with or without PET, and of alternate methods for the assessment of myocardial viability in patients with coronary

artery disease, which is the most widespread clinical application of the approach.

## Assessment of myocardial viability: Is it clinically relevant?

Although most akinetic segments of ventricular myocardium correspond to infarcted regions, a variable amount of myocytes survive the acute ischemic insult and remain 'at risk', because critical narrowing or occlusion of the infarct vessel in most cases persists without intervention. The ultimate fate of surviving myocardium will largely depend on residual perfusion, energy demands, and the metabolic and hormonal environment, among other factors. R. Ferrari traces in his article the different possible fates of myocytes that have suffered an ischemic insult. A major point emerging from the subsequent articles, by J.J. Bax et al., and F.C. Visser and M. Marber, is that detection of criteria of viability in a chronically akinetic region by metabolic imaging represents a strong argument in favor of revascularization, for a number of reasons: First, the region may recover contractile function, at least to some extent, and thereby not only improve symptoms of heart failure, but also reduce morbidity and mortality. Second, viable myocardium in a critically perfused region may represent a substrate for life-threatening arrhythmia. Third, residual viability in akinetic regions tends to disappear gradually, even without recurrence of an acute coronary event. Because operative mortality in coronary patients with poor ventricular function is lower in the presence of viable myocardium, timely intervention may reduce the risk. Finally, preservation of even a small layer of viable

myocardium in an infarcted region may prevent progressive remodeling and failure.<sup>3</sup> Taken together, available information suggests that assessment of tissue viability is of clinical relevance, allowing better stratification of coronary patients with compromised left ventricular function and optimizing selection of high-risk patients for invasive procedures.

### Metabolic approach versus “standard” diagnostic methods

A number of properties of intact myocytes, in addition to sustained metabolic activity, are currently used to assess myocardial viability by different imaging modalities. In their articles F.C. Visser and M. Marber, and U. Schricke and M. Schwaiger, compare metabolic imaging to other approaches that have been proposed for this purpose, including nuclear echocardiographic and MRI techniques. Only a few studies have directly compared different methods. The overall picture that emerges is that metabolic imaging has a high sensitivity for the detection of viable myocytes. This is not entirely surprising because (1) small amounts of viable myocardium may be sufficient to ‘light-up’ at metabolic imaging but insufficient to detectably improve contractile function in response to  $\beta$ -adrenergic stimulation; and (2) myocytes in chronically hibernating regions often exhibit profound changes in the phenotype with loss of myofibrils, and consequently the ability to contract. The question whether all metabolically active myocytes in hibernating myocardium bear the potential to recover contractile function remains to be answered.

### Is metabolic imaging necessary for patient management?

I am not aware of any clinical practice guideline on the management of patients with coronary artery disease which includes metabolic imaging as an obligatory step for decision making. The ‘state of the art 2000’ of metabolic imaging published in this issue of *Heart and Metabolism* strongly suggests that assessment of myocardial viability may provide incremental information relevant for optimal management of selected coronary artery disease patients, in particular those with compromised ventricular function. The prevalence of heart failure, which in most cases is a late complication of coronary artery disease, will appreciably increase during the next decades.<sup>4</sup> Improved identification of patients in which progressive remodeling can be slowed by revascularization procedures may not only enhance the risk/benefit ratio, but also lower the cost/benefit relationship of interventional strategies. Therefore the overall benefit may well outweigh the costs associated with metabolic imaging.

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# Metabolic changes in stunning and hibernation

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Myocardial ischemia is very complex and, unless interrupted by early reperfusion, will culminate in cell death. Although a prerequisite for survival, reperfusion is not without hazard, however. Paradoxically, although ischemia is 'bad' and reperfusion is 'good', ischemia can be protective (preconditioning and a trigger for hibernation) and reperfusion can be 'bad' (reperfusion injury). Understanding, manipulating and exploiting these processes requires a detailed knowledge of the molecular mechanisms of ischemia and reperfusion. Much has already been learnt but much more remains to be discovered. With that knowledge we may be able to make a major impact on the devastating consequence of coronary heart disease.

## Different facets of myocardial ischemia

There is no simple definition of ischemia. In an attempt to address the problem, Hearse invited 31 eminent cardiologists, all experts in the field, to provide a brief definitive definition.<sup>1</sup> The result was a multitude of differing and sometimes conflicting suggestions, ranging from just a few to several hundred words in length. Hearse then proposed that a fundamental distinction should be made between 'physiological' and 'biochemical' ischemia.<sup>1</sup> Although this is an oversimplification of a complex issue, a region of the heart may be considered as physiologically ischemic when, as a consequence of flow reduction, it is

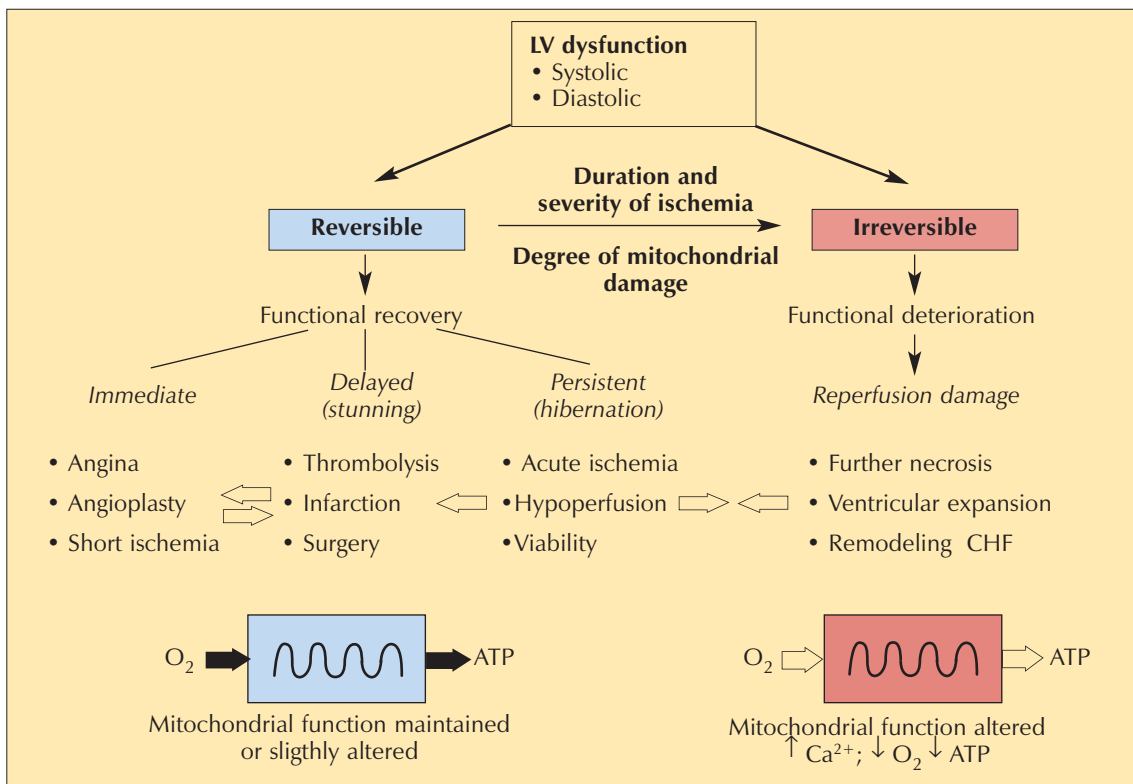


Figure 1. Schematic representation of the possible outcomes of myocardial ischemia.

unable to maintain normal contractile function.<sup>1</sup> This is how a clinical cardiologist perceives ischemia. He **or she** knows that it is linked, at best, with regional left ventricular dysfunction of both a systolic and diastolic nature (*Figure 1*). If the period of ischemia is short, there is no major molecular damage and functional impairment is reversible on reperfusion. However, if the ischemia is more severe or more prolonged, irreversible molecular damage could occur, recovery on reperfusion becomes impossible, and necrosis inevitably develops. This key transition might occur within minutes of the onset of ischemia, or take up to several hours depending on a multitude of factors (the underlying metabolic rate probably being the most important). For the clinical cardiologist this is, in turn, determined by the extent of residual flow, the underlying heart rate, the degree of hemodynamic change (such as an increase in pre- and after- load, wall stress), and by the effects of any accompanying neuroendocrine activation. This physiological ischemia, characterized by down-regulation of contraction in the absence of molecular changes, can also be considered a conservative adaptive response by the myocyte that down-regulates its contraction independently of extracardiac signals and, in so doing, reduces its energy needs in an attempt to maintain viability. A reserve reperfusion injury – the so-called myocardial stunning – has recently been discovered.

In contrast, in biochemical ischemia,<sup>1</sup> possibly in response to a series of complex and predominantly extracardiac neurohormonal signals (activated to ensure the maintenance of pump function and cardiac output), the myocyte will, at a high cost, succumb to a series of cellular mechanisms that will attempt to maintain contractile function despite impairment to the oxygen supply. In consequence, the supply of energy fails to match consumption, and intracellular equilibrium (steady-state metabolism) is sacrificed, initiating a cascade of increasingly severe metabolic perturbations. The cell will then become ‘metabolically distressed’<sup>1</sup> and, unless interrupted by early reperfusion, biochemical ischemia will inevitably progress towards cell

death. As indicated in *Figure 1*, the mitochondria are the organelles most likely to be involved in the transition of reversible ischemia to definitive cell death. This is, perhaps, not surprising since these organelles play a fundamental role in cellular energy production (the ATP turnover of the human heart exceeding 30 kg per day), and in maintaining intracellular ionic homeostasis – the other key process which is threatened by ischemia.

### Reperfusion of ischemic myocardium: an important determinant in the transition from ischemia to cell death

Our understanding of the complexities of ischemia and tissue injury is further complicated by the need to reperfuse the tissue in order to determine whether ischemic damage is reversible or irreversible. Some, but not all, investigators believe that reperfusion itself might be detrimental and able to inflict injury over and above that attributable to the ischemia it is expected to remedy.<sup>2</sup> Other investigators, however, question the existence of ‘reperfusion-induced injury’.<sup>3</sup> This question will not be discussed here. Instead, the concept that ischemia is not a static condition and that reperfusion is a part of the continuum of coronary artery disease will be explored. Such reperfusion might, however, occur at different times during the transition from angina to myocardial infarction, and have several different outcomes such as early or delayed recovery (stunning), no recovery or some recovery (hibernation).

### A perfect match between physiological and biochemical ischemia maintains viability

During short periods of ischemia, for example in angina, there is a perfect match between biochemical and mechanical activity; this allows viability to be maintained. Restriction of coronary flow results in a rapid down-regulation of contraction and eventually quies-

cence. This is due to the effects of intracellular acidosis, which develops within seconds of the induction of ischemia and reduces calcium movements within the sarcolemma, sarcoplasmic reticulum and myofilaments.<sup>4</sup> Shortly after, the energy charge of the myocyte is reduced: creatine phosphate declines faster and to a greater extent than ATP. Anaerobic metabolism, as shown by lactate release in the coronary effluent, develops and contributes to the formation of limited amounts of ATP by oxygen-independent, substrate-level phosphorylation. Taken together, these findings suggest the occurrence of biochemical as well as physiological ischemia. Both down-regulation in contraction (and therefore in ATP consumption) and increased anaerobic ATP production explain why the

decline in tissue ATP after the onset of ischemia is not immediate. The availability of this residual energy supply is essential to maintain cellular viability. Reperfusion at this stage results in a recovery of high-energy phosphate production, which, in turn, indicates that the mitochondria are still functionally intact and capable of normal aerobic metabolism; this is linked to a recovery of mechanical function which may be immediate or somewhat delayed.

This sequence of metabolic and functional events is not restricted to experimental models, but also occurs at the clinical level, for example, during angina induced by atrial pacing. *Figure 2* shows that in coronary artery disease patients with angina, increasing heart rate (and, therefore, increasing the heart's

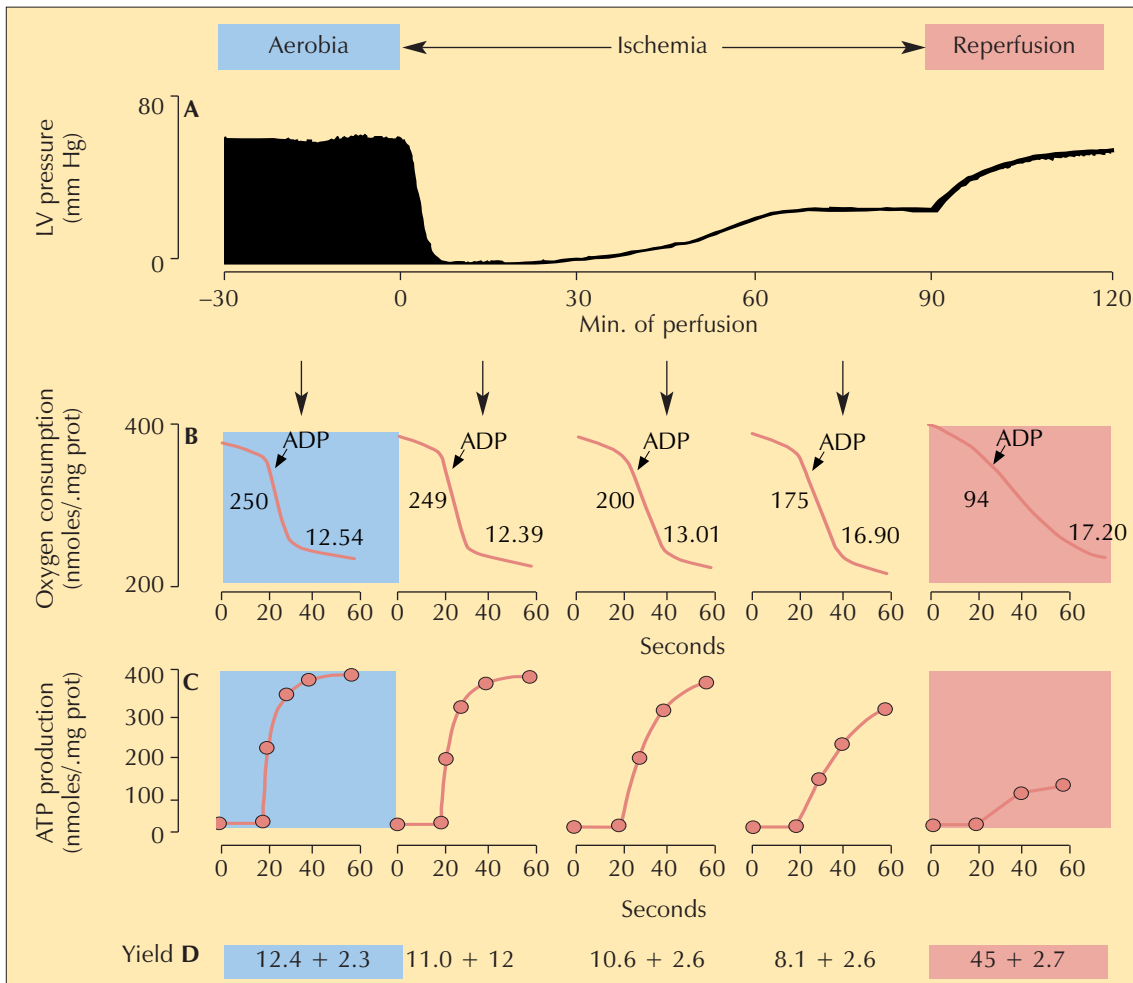


Figure 2. Metabolic changes occurring during early phases of ischemia in coronary artery disease patients.

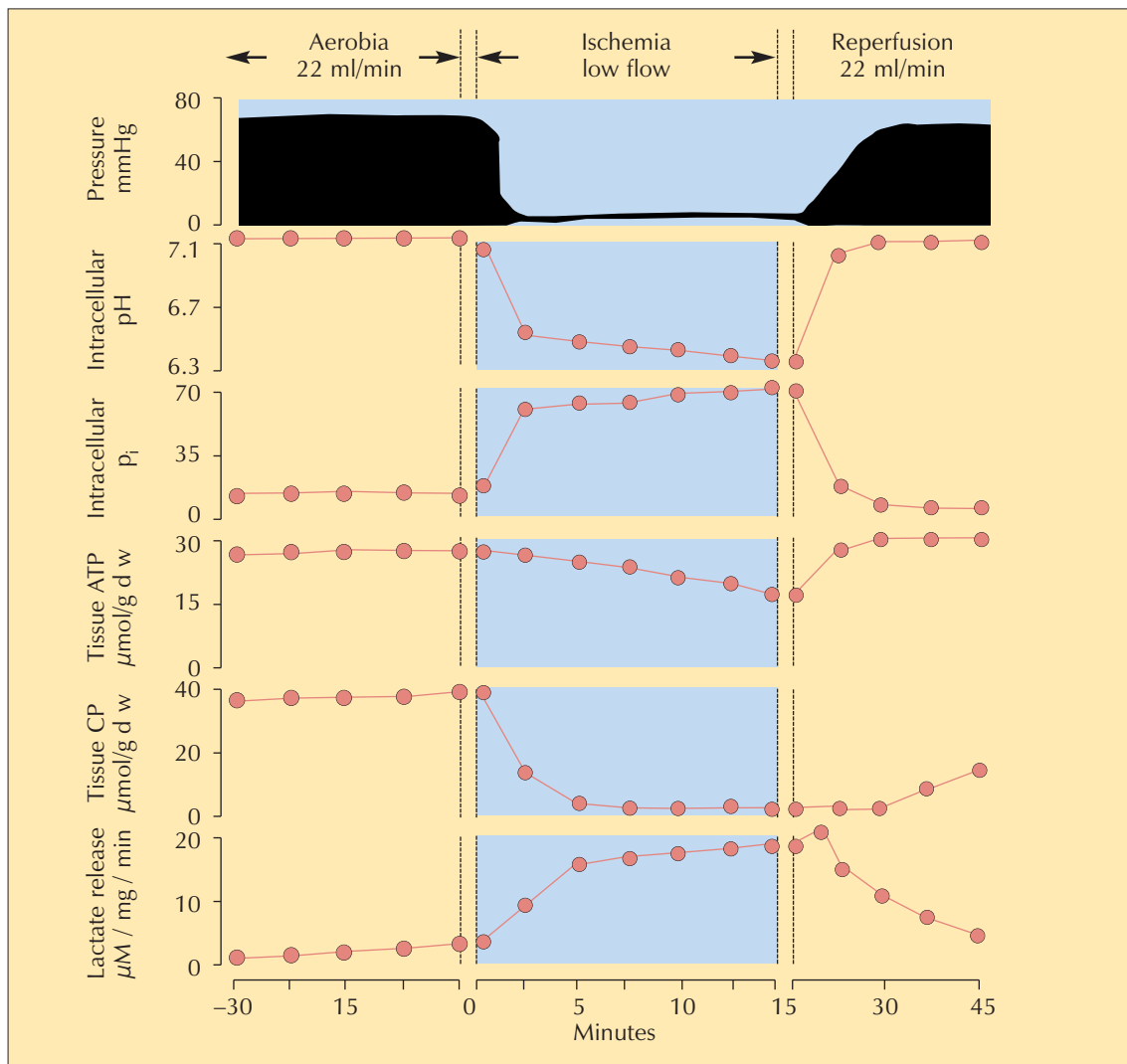


Figure 3. Effects of 90 min of ischemia followed by 30 min of reperfusion on mitochondrial function. Paced, isolated perfused rabbit hearts were used for these experiments. Under control and reperfusion conditions the hearts were perfused at a mean coronary flow of 25 ml/min. Ischemia was induced by reducing coronary flow to 1 ml/min. A: Typical example of a left ventricular pressure tracing from a whole heart subjected to ischemia and reperfusion. B and C: Typical examples of isolated mitochondrial tracing for oxygen consumption and ATP production. The mitochondria were isolated from hearts which had been aerobic for 30 min, ischemic for 30, 60 or 90 min and reperused for 30 min. The numerical values reported in the oxygen consumption tracing represents rates (nmol oxygen/mg protein/min) consumed by the isolated mitochondria during states III and IV of respiration. Glutamate was used as respiratory substrate.

energy requirement to the extent that it is no longer met by the supply) results in a reduction of coronary sinus pH, which indicates the occurrence of myocardial acidosis. This is then followed by an increase in coronary sinus lactate (which is indicative of the development of anaerobic metabolism), and in a down-regulation of regional contraction

(revealed by a reduction of ejection fraction, which is suggestive of systolic dysfunction). All these biochemical and mechanical events precede the occurrence of angina. Once the heart rate has returned to its basal level and the ischemia, therefore, no longer persists, coronary sinus pH and lactate return to normal values and left ventricular systolic func-

tion improves. However, the functional recovery is not immediate because of the presence of stunning.<sup>5</sup> Under such circumstances, viability is maintained but evidence of the ischemic insult persists for as long as the recovery of function does not match that of metabolism.

### Early reperfusion causes stunning: lingering evidence of preceding physiological and biochemical ischemia

There is now convincing evidence that the myocardium that has been reperfused after a short period of ischemia is characterized by a variety of unfavourable (but non-lethal) cellular changes that, given sufficient time, will revert to normal. The most prominent of these changes is *myocardial stunning*, which is the prolonged contractile dysfunction that occurs during reperfusion despite the absence of irreversible injury.<sup>5,6</sup> The duration of the dysfunction greatly exceeds that of the antecedent ischemia. For example, after 15 min of ischemia in dogs, myocardial function remains depressed for 24 hours.<sup>7</sup> However, by definition this form of injury is fully reversible, provided sufficient time is allowed. Interventions such as isotropic agents can override stunning and other interventions (such as anti-oxidants) can prevent its occurrence.<sup>6</sup>

A number of candidate mechanisms for stunning have been investigated; these include: an impaired ability to resynthesize high-energy phosphates, functional sympathetic denervation, heterogenous impairment of regional perfusion, abnormal electrical activation, loss of creatine kinase activity, damage to the collagen matrix, leukocyte activation, and decreased sensitivity of myofilaments to calcium. However, the two most plausible mechanisms relate to free radical induced injury during the early moments of reperfusion and impaired calcium homeostasis.

Numerous studies suggest that oxygen-derived free radicals contribute to post-ischemic dysfunction.<sup>9</sup> In dogs subjected to 15 min of coronary occlusion, stunning is reduced by drugs that scavenge oxygen radi-

cals or prevent their generation. The generation of free radicals in the stunned myocardium has been directly demonstrated with electron paramagnetic resonance spectroscopy, and the attenuation of radical generation has been shown to result in the attenuation of contractile dysfunction.<sup>8</sup> Although there is strong evidence that reactive oxygen intermediates play a major role in the pathogenesis of myocardial stunning, there is also evidence that this phenomenon is related to abnormalities of calcium homeostasis.<sup>6</sup> It is important to emphasize that calcium and free radical mechanisms are not mutually exclusive but may represent two facets of the same phenomenon. Thus, Bolli has suggested that oxygen free radicals may cause sarcolemmal and sarcoplasmic reticulum dysfunction and perturbations of calcium distribution. The latter, in turn, could exacerbate the damage initiated by the radicals and indeed could promote the production of further radicals.<sup>6</sup>

### The transition from ischemia to cell death: when biochemical ischemia overrides physiological ischemia

If coronary flow remains severely reduced, the myocardium will remain quiescent but nonetheless biochemical ischemia intensifies and proceeds towards irreversible damage. From the metabolic point of view, prolongation of ischemia results in further decrease in intracellular pH and in a progressive increase of resting pressure and myocardial stiffness. The early increase in lactate is followed by a decline together with a further decrease in tissue content of ATP and CP. This supports the view that, after an initial stimulation, anaerobic glycolysis is inhibited by the more severe intracellular acidosis. At this stage profound ionic changes occur with a deletion of intracellular  $K^+$  and  $Mg^{2+}$  and an increase of  $Na^+$  and of cytosolic  $Ca^{2+}$ . Interestingly, even after prolonged ischemia, total tissue calcium concentration is unchanged but mitochondrial calcium is increased, indicating an intracellular redistribution of the ion. Isolated mitochondrial function, however, is then main-

tained since only a slight reduction in the initial rate of ATP production is observed. In spite of this, reperfusion does not restore mitochondrial or myocardial function. On the contrary, it produces a further increase of stiffness and non-recovery of contractility or of tissue ATP and CP concentrations. During reperfusion there is a significant and sustained release of lactate, ions and CPK, massive influx of calcium and severe mitochondrial damage, suggesting that late reperfusion causes not only a wash-out of these substances but also an exacerbation of their release.<sup>6</sup> These findings indicate that a lesion of the cell membrane has occurred, leading to a breakdown of the permeability barrier to ions such as  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$ , as well as to larger molecules such as CPK, and that mitochondria are using the restored oxygen for buffering cytosolic  $\text{Ca}^{2+}$  rather than for ATP production. For this reason, mitochondria are supposed to play a central role in reperfusion damage. It appears that these organelles are quite resistant to ischemic damage; however, the presence of residual phosphorylation capacity in mitochondria during ischemia is associated with irreversible damage during reperfusion such that, paradoxically, mitochondrial uncouplers can afford cardiac protection.<sup>9</sup>

From this it follows that residual mitochondrial function during ischemia might be interpreted as good or bad. This apparently contradictory concept arises from the finding that, on the one hand, intact, normally functioning mitochondria are essential for the recovery of mechanical function during reperfusion but, on the other hand, the inhibition of the respiratory chain or the addition of uncouplers of oxidative phosphorylation are able to limit the extent of enzyme release in various models of myocardial damage.<sup>9</sup> These findings suggest the complex scenario that the restoration of ATP production by mitochondrial oxidative phosphorylation is essential for myocardial recovery, but, at the same time, this mitochondrial activity can also contribute to those processes which produce cell necrosis. Understanding these mechanisms is important as, in an *in vivo* condition such as during evolving myocardial infarction, a continuous sequence

of ischemia and reperfusion is likely to occur as collateral flow develops.

### Late reperfusion of hibernating myocardium and recovery: *physiological ischemia without biochemical ischemia*

The term 'hibernation' has been borrowed from zoology and implies an adaptive reduction of energy utilization through reduced activity under conditions of a reduced energy supply. In the context of coronary artery disease, myocardial hibernation was originally seen as a *chronic, adaptive* reduction of myocardial contractile function in response to a reduction of myocardial blood flow. It was also viewed as a condition where there would be a complete recovery of contractile function upon the restoration of flow. Thus, in the concept of myocardial hibernation, the observed chronic reduction of myocardial contractile function is not regarded as the result of a persistent energetic deficit, but instead as a regulatory event which acts to avoid an ongoing energy deficit and thereby maintain myocardial integrity and viability.

Interestingly, the concept of myocardial hibernation does not originate in the laboratory instead it is entirely founded on clinical experience when, in the early 1980s, Rahimtoola reviewed the results of coronary bypass surgery trials and identified a subset of patients with coronary artery disease and chronic left ventricular dysfunction that improved upon revascularization.<sup>10</sup> Whereas originally the idea of an adaptive reduction of contractile function in response to a reduction in blood flow was straightforward and simple, the situation of chronic, yet reversible contractile dysfunction in the setting of coronary artery disease was not recognized and was seen as enormously complex and controversial.

The introduction of the concept of hibernation has challenged the traditional view that the extent of chronic contractile dysfunction necessarily reflects the amount of infarcted tissue. In hibernation, preservation of viability

rather than the occurrence of necrosis accounts for the observed reduction in function. In view of the preserved viability of the tissue, hibernation is a key factor in assessing the potential benefit that might be expected from reperfusion/revascularization. Hibernating myocardium must be recognized and identified by appropriate diagnostic procedures and requires decisions by the responsible cardiologist for the selection of patients who will benefit from interventional reperfusion or surgical revascularization. Of course, hibernation is only one of several important aspects which must be considered in the selection of patients who will benefit from reperfusion or revascularization, and many patients with coronary artery disease and no evidence of hibernating myocardium will also benefit.

A hibernation-like metabolic adaptation to a severe sustained low-flow ischemia has recently been reported in studies with isolated perfused rabbit hearts in which there was a preceding short episode (10 min) of zero-flow ischemia. In these hearts, the early decline in contractile function was more pronounced and significantly faster than in control hearts that did not have the brief episode of zero-flow ischemia. The rapid decline in contractile function (physiological ischemia) during the brief episode of no-flow ischemia was accompanied by a greater decrease in interstitial<sup>4</sup> and intracellular<sup>11</sup> pH, and the contractile quiescence was attributed to a faster development of myocardial acidosis. Interestingly, interstitial and intracellular pH during the subsequent low-flow ischemia remained mildly reduced whereas these pH values were markedly decreased when low-flow ischemia was not preceded by zero-flow ischemia. During low-flow perfusion there was no lactate release, suggesting that biochemical ischemia did not occur. During reperfusion following the sustained ischemia, only a transient creatine kinase leakage occurred in the hearts with preceding zero-flow ischemia. Thus, the establishment of the experimental form of myocardial hibernation requires an initial period of zero-flow ischemia, during which time the rapid decrease in interstitial and intracellular pH trigger the decrease in contractile

function and thereby facilitates the restoration of the balance between energy supply and energy demand. In other studies, in anaesthetized swine hearts in situ, the size of infarcts arising as a consequence of sustained (90 min) zero-flow ischemia was reduced by a short (10 min) period of no-flow ischemia immediately before the sustained ischemia.<sup>12</sup> A reduction in infarct size was also achieved by a 70% reduction in flow for 30 min preceding 60 min of total coronary artery occlusion.<sup>13</sup> These experimental studies attribute a potentially important role to an initial stimulus of severe ischemia as being critical to 'triggering' the development of a protective state with preserved viability during a subsequent period of sustained ischemia. Whether or not such an initial stimulus/trigger of severe ischemia represents a mandatory link between hibernation and ischemic preconditioning is unclear at present,<sup>14</sup> but it would support the hypothesis that hibernating myocardium, at least most of the time, might not be biochemically ischemic but will be physiologically ischemic.<sup>15</sup>

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# Metabolic imaging in the evaluation of myocardial ischemia and viability

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## Introduction

The number of patients presenting with chronic heart failure secondary to coronary artery disease and left ventricular (LV) dysfunction is increasing rapidly. It has recently been estimated that 4.7 million patients in the USA have chronic heart failure and the incidence of coronary artery disease in these patients may be as high as 70%.<sup>1</sup>

The long-term prognosis of patients with heart failure is extremely poor; data from the Framingham Heart Study documented a 5-year survival rate of 25% in men and 38% in women who developed heart failure.

Therapeutic options in these patients include medical therapy, heart transplantation or revascularization. Despite the optimization of medical therapy (diuretics, digoxin, ACE inhibitors, beta-blockers, spironolactone), the long-term prognosis remains poor. The long-term results with heart transplantation are excellent, but the limited number of donor hearts is greatly exceeded by the increasing demand. The third option (revascularization) can be an alternative, although the procedure is accompanied by a much higher risk for (peri-)operative events than in patients with normal LV function.<sup>2</sup> Data from the Collaborative Study in Coronary Artery Surgery in 6630 patients, revealed a (peri-)operative mortality of 1.9% in patients with a preserved LV function (LV ejection fraction [LVEF] >50%) compared with 6.7% in patients with an LVEF <20%.<sup>2</sup>

Conversely, a substantial number of patients show an improvement in LVEF after revascularization. Elefteriades et al<sup>3</sup> evaluated LVEF before and after surgical revascularization in 68 patients with depressed LVEF and demonstrated a significant improvement in LVEF in

roughly 60% of these patients. Since LVEF is an important prognostic parameter, improvement in LVEF may translate into improved survival.

Based on these considerations, identification of patients who may potentially benefit from revascularization is mandatory in order to justify the increased risk of (peri-)operative events. The postoperative improvement in LVEF has been related to the preoperative presence of viable myocardium.<sup>4</sup> Accordingly, assessment of myocardial viability has become an important component of the diagnostic and prognostic **workup** of patients with ischemic cardiomyopathy.

Over the past two decades a number of diagnostic modalities have been developed for the identification of viable myocardium.<sup>4</sup> These modalities are based on the detection of different characteristics of viable myocardium, including residual metabolic activity, cell membrane integrity, intact mitochondria or inducible contractile reserve. Residual metabolic activity (oxidative or anaerobic) can be evaluated by labeling different myocardial substrates with radionuclides (*Figure 1*). The clinically most relevant radionuclides include <sup>11</sup>C-acetate (to assess oxidative metabolism), <sup>123</sup>I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP, to assess free fatty acid utilization) and F18-fluorodeoxyglucose (FDG, to evaluate glucose utilization).<sup>4,5</sup> Cell membrane integrity can be evaluated using thallium-201, intactness of mitochondria can be studied with technetium-99m sestamibi, and contractile reserve can be probed with 2D echocardiography or MRI during stepwise infusion of dobutamine.

In this article, the use of radionuclides for the **noninvasive** assessment of myocardial metabolism will be reviewed. Following a

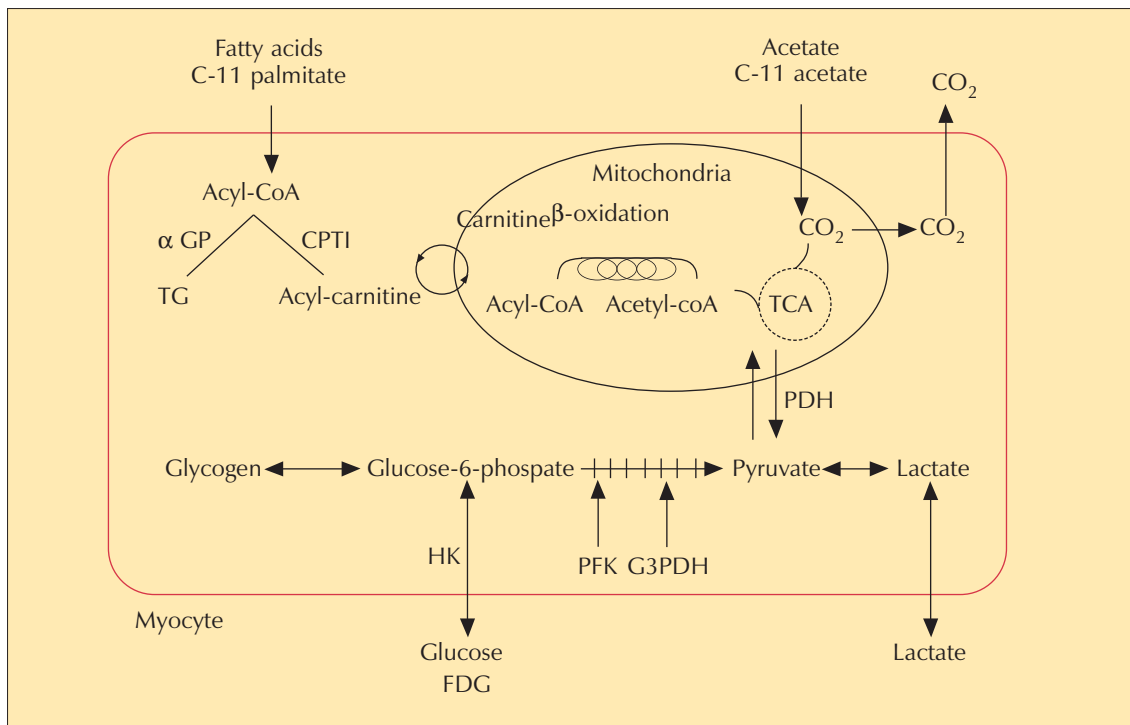


Figure 1. Schematic presentation of metabolic pathways of myocardial substrate metabolism. Positron emitting radionuclides such as <sup>11</sup>C-palmitate, <sup>11</sup>C-acetate and <sup>18</sup>F-labeled deoxyglucose (FDG) are tracers of the metabolic rate of important energy substrates such as free fatty acids and glucose. In addition, the single-photon emitting agent <sup>123</sup>I-labeled 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP, not shown in this figure) also traces free fatty acid metabolism. α GP, alpha-glycerol phosphate; CoA, coenzyme A; CPT-1, carnitine-palmitoyl-transferase; HK, hexokinase; G3PDH, glyceraldehyde-3-phosphate dehydrogenase; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; TCA, tricarboxylic acid cycle; TG, triglycerides. (Reproduced from reference 53 with permission.)

brief summary on cardiac metabolism, the role of the three radionuclides (<sup>11</sup>C-acetate, BMIPP and FDG) will be discussed.

### Cardiac metabolism

The heart has the ability to metabolize a wide variety of substrates such as free fatty acids, glucose, lactate, pyruvate, ketone bodies and amino acids. Under normal resting conditions, metabolism is mainly oxidative, with free fatty acids and glucose being the major sources of energy. The preferred substrate depends on arterial substrate concentrations (dietary conditions), hormonal factors (mainly insulin) and workload. For example, in the fasting state free fatty acids are primarily utilized for cardiac energy production, whereas in the postprandial state glucose becomes the preferred substrate.

Under ischemic conditions with decreased oxygen delivery, oxidative metabolism of free fatty acids is decreased and exogenous glucose becomes the preferred substrate for the myocardium. Depending on the degree of residual oxygen availability, glucose may predominantly be metabolized anaerobically as evidenced by increased lactate release. The amount of energy produced by anaerobic glycolysis may not be adequate to maintain contractility but may be sufficient to preserve the cellular integrity. However, if perfusion is diminished below a critical threshold level, tissue concentrations of lactate and hydrogen ions rise and inhibit glycolysis.<sup>6</sup> This results in loss of ion concentration gradients across the cell membrane, followed by cell membrane disruption and cell death.

Accordingly, information on the use of different metabolic substrates is highly valuable

in evaluating the 'viability status' of the myocardium.

### Assessment of oxidative metabolism: $^{11}\text{C}$ -acetate

#### $^{11}\text{C}$ -acetate as a tracer

Acetate is easily labeled with  $^{11}\text{C}$  and in contrast to other metabolic tracers, such as FDG and labeled fatty acids,  $^{11}\text{C}$ -acetate is directly taken up by the tricarboxylic acid (TCA) cycle and metabolized to  $\text{CO}_2$  and water.  $^{11}\text{C}$ -acetate used in nuclear medicine is usually labeled in the C-1 position to avoid metabolic trapping in amino acid pools and the TCA cycle. Uptake of  $^{11}\text{C}$ -acetate after intracoronary and intravenous administration is avid and fast, and dependent on blood flow. Metabolism is in principle only dependent on TCA cycle activity. The clearance rate of  $^{11}\text{C}$  activity from the heart after administration of the tracer is a direct reflection of the activity of the TCA cycle. Because TCA cycle activity is directly coupled to myocardial oxygen consumption ( $\text{MVO}_2$ ), myocardial clearance rates of  $^{11}\text{C}$ -acetate reflect oxidative metabolism. Clearance of  $^{11}\text{C}$ -acetate is almost independent from the substrate that is used as the main fuel by the heart at the moment of administration of the tracer, because there is only a variation of approximately 4% in production of the reducing equivalents ( $\text{NADH} + \text{H}^+$  and  $\text{FADH}_2$ ) used in oxidative phosphorylation when either glucose or free fatty acids are used as the substrate.

Time-activity curves obtained from regions of interest in  $^{11}\text{C}$ -acetate studies consist of two parts: a build-up phase and a clearance phase. Usually, the initial part of the study (the build-up phase of activity) lasts around 5 min, after which a steep decay occurs. Data of the uptake phase have been used for determination of myocardial blood flow, either qualitatively by determining peak myocardial values or quantitatively by modeling. Although blood flow and metabolism are usually tightly coupled, there is still a variation in blood flow at a certain level of metabolism, especially in patients with

ischemic heart disease.<sup>7</sup> This implies that peak myocardial values after  $^{11}\text{C}$ -acetate injection are correlated, but not tightly, with myocardial clearance rates of  $^{11}\text{C}$ -acetate.

Clearance of  $^{11}\text{C}$ -acetate from the heart is exponential and consists of one exponential at low cardiac workloads and two exponents at higher workloads. Because of the positron emission of  $^{11}\text{C}$  and the rapid clearance of  $^{11}\text{C}$ -acetate from the myocardium, a study is best performed using PET equipment when regional information is important; however, one study used gamma-cameras equipped with high-energy collimators to determine global  $^{11}\text{C}$ -acetate clearance from the myocardium.<sup>8</sup>

#### Relation of $^{11}\text{C}$ -acetate clearance to $\text{MVO}_2$

Initial studies validating acetate as a measure of  $\text{MVO}_2$  were performed with  $^{14}\text{C}$ -acetate and a direct relation was found between  $^{14}\text{C}$ - $\text{CO}_2$  production and  $\text{MVO}_2$ .<sup>9</sup> The clearance rate in the venous effluent of  $^{14}\text{C}$ - $\text{CO}_2$  was similar to that of externally measured clearance from the myocardium of  $^{11}\text{C}$ -activity, measured with gamma-probes after simultaneous injection of  $^{14}\text{C}$ - and  $^{11}\text{C}$ -acetate.<sup>9</sup> The clearance rate was found to be independent of myocardial substrate usage.<sup>10</sup> In later experiments, myocardial clearance rates measured with PET were related to measured  $\text{MVO}_2$  and tight correlations were found,<sup>10</sup> as well as with the rate-pressure product (RPP). In animals, a bi-exponential clearance rate was usually found, whereas clearance was mono-exponential at rest in humans.<sup>11</sup> This can be explained by the lower workload of the hearts of larger mammals (lower frequency, but also lower wall tension). With dobutamine stimulation, clearance rates usually become bi-exponential.<sup>11,12</sup> However, the second exponential is extremely slow ( $0.005$ – $0.01 \text{ min}^{-1}$ ) and to determine this rate adequately, scanning times of 1–3 h are necessary, which is impractical. Therefore, in humans usually mono-exponential curve-fitting procedures were used.

The RPP is usually used to determine car-

Table 1. Relation of mono-exponential curve-fits of <sup>11</sup>C-acetate clearance to the RPP in humans: results from linear regression analysis.

Reference	No. of experiments	Linear relation between RPP and mono-exponential fitting of <sup>11</sup> C-acetate		
		Slope (10 <sup>-6</sup> )	Intercept	r
Armbrecht et al. <sup>15</sup>	22	5.89	0.014	0.91
Tamaki et al. <sup>11</sup>	18	6.82	0.014	0.87
Tamaki et al. <sup>13</sup>	28	6.72	0.013	0.86
Krivokapich et al. <sup>12</sup>	22	8.5	-0.01	0.94
Vanoverschelde et al. <sup>14, a</sup>	16	5.14	0.022	0.87

<sup>a</sup>Figures calculated from data provided in the original publication.

diac work and thus the MVO<sub>2</sub> in humans. Mono-exponential clearance rates in humans were closely correlated to the RPP.<sup>11-16</sup> The relationships determined are shown in Table 1. There is a rather large variation between the different reports, limiting the universal use of <sup>11</sup>C-acetate clearance to determine oxygen consumption based on these relationships. A probably more accurate approach to determine MVO<sub>2</sub> from the <sup>11</sup>C-acetate clearance is the use of tracer kinetic modeling. This has been validated by Sun et al.<sup>17</sup>, but needs confirmation in other studies.

### <sup>11</sup>C-acetate in ischemia and viability

Acetate has been extensively used in studies evaluating ischemia and myocardial infarction. In animals, it was observed that myocardial TCA cycle activity was reduced immediately after occlusion of a coronary artery and subsequent release, but recovered in the following days to weeks.<sup>18</sup> There was a significant correlation between the recovery of TCA cycle activity and the recovery of function.<sup>18,19</sup> The effect of dobutamine on stunned myocardium, showing recovery of TCA cycle activity, was found by Hashimoto et al.,<sup>20</sup> together with recovery of function.

In humans, <sup>11</sup>C-acetate clearance was reduced in the central area of myocardial infarction, with gradual normalization of the clearance rates in regions more distant from its center.<sup>21</sup> Also in patients with reperfusion therapy after myocardial infarction a reduction in oxidative metabolism could be demon-

strated.<sup>22</sup> Relatively preserved <sup>11</sup>C-acetate clearance (in relation to perfusion) was associated with recovery of function.<sup>22</sup>

In patients with chronic LV dysfunction due to coronary artery disease or previous infarction, recovery of function was found in areas with a relatively preserved <sup>11</sup>C-acetate metabolism.<sup>23</sup> In addition, dobutamine increased <sup>11</sup>C-acetate clearance in areas showing recovery of function after revascularization, in contrast to areas that did not.<sup>24</sup> These observations led to investigations to predict recovery of function based on <sup>11</sup>C-acetate clearance<sup>25,26</sup> (Table 2). These studies used absolute cut-off values of <sup>11</sup>C-acetate clearance to predict recovery of function, irrespective of myocardial workload. Neither of the studies used <sup>11</sup>C-acetate clearance normalized to that of myocardium with normal wall motion. Nevertheless, sensitivity and specificity of <sup>11</sup>C-acetate to predict recovery of function after revascularization were 81% and 61%, respectively. Compared with the sensitivity and specificity of FDG PET (88% and 73% respectively, see below),<sup>27</sup> absolute <sup>11</sup>C-acetate clearance may not be as accurate for the prediction of recovery of function after

Table 2. <sup>11</sup>C-acetate to predict recovery of function post-revascularization.

Reference	No. of segments	Sensitivity (%)	Specificity (%)
Gropler et al. <sup>25</sup>	116	87 (40/46)	71 (50/70)
Wolpers et al. <sup>26</sup>	114	77 (46/60)	48 (26/54)
Pooled data	230	81 (86/106)	61 (76/124)

revascularization. However, additional studies employing normalized clearance rates may improve the accuracy of  $^{11}\text{C}$ -acetate imaging for the prediction of functional recovery after revascularization.

### Assessment of oxidative metabolism: free fatty acids

Since long-chain non-esterified free fatty acids are the main energy source for the normoxic myocardium, various radiolabeled free fatty acid analogues have been developed for **in vivo** scintigraphy.  $^{11}\text{C}$ -palmitate in combination with PET is considered to be the gold standard for **noninvasive** evaluation of cardiac free fatty acid utilization. Following intravenous administration,  $^{11}\text{C}$ -palmitate is avidly taken up by the myocardium. Therefore, 3–5 min after tracer administration, myocardial distribution shows a good correlation with perfusion. In normal myocardium, clearance shows a bi-exponential pattern, with a rapid early phase corresponding to beta-oxidation of  $^{11}\text{C}$ -palmitate with release of  $^{11}\text{C}$ - $\text{O}_2$  and after 20–30 min a slower second phase mainly reflecting incorporation of  $^{11}\text{C}$ -palmitate into the lipid pool.<sup>28</sup> The complexity, high costs and the observation that back-diffusion of non-metabolized  $^{11}\text{C}$ -palmitate during ischemia contaminated the early clearance phase (and thus data interpretation),<sup>28</sup> have limited widespread use of  $^{11}\text{C}$ -palmitate.

Alternatively, radioiodinated fatty acids have been advocated for the **noninvasive** investigation of cardiac free fatty acid utilization in humans (see for an overview ref 29). Iodine-123 has physical properties (peak energy 159 keV, half-life 13.2 h) that allow acquisition with conventional gamma-cameras and the iodine molecule resembles stereometrically a methyl group. In the past two decades a variety of radioiodinated fatty acids have been developed to study free fatty acid metabolism. Initially, straight-chain iodinated fatty acids have been studied, in which iodide or an iodinated phenylring was introduced at the terminal end of the fatty acid chain. Because of the relatively rapid turnover, limiting the use for

SPECT imaging, the background activity and backdiffusion during ischemia, these iodinated fatty acids are not used in clinical cardiology.

To increase myocardial retention, methyl-branching of free fatty acids was introduced by Knapp et al.<sup>30</sup> The radioiodinated 3-monomethyl-substituted analogue, BMIPP, exhibits myocardial clearance slow enough to permit regional distribution studies by SPECT.

### BMIPP as a tracer

Despite its modified structure, it was demonstrated in the initial biodistribution studies<sup>30</sup> that myocardial uptake of BMIPP is similar to that of natural free fatty acids. Fujibayashi et al.<sup>31</sup> observed that in normal canine myocardium 74% of the intracoronary administered dosage of BMIPP was extracted with a subsequent retention of 65%.

Following myocardial uptake, BMIPP is activated to BMIPP-CoA. Thereafter it is mainly incorporated into triacylglycerols.<sup>30</sup> The remaining (smaller) part is catabolized.<sup>32</sup> BMIPP metabolism also depends on substrate availability.<sup>32</sup> Following fasting, glucose plasma levels are diminished, while free fatty acid levels are high. As a consequence, cardiac uptake of BMIPP is favored under these circumstances and therefore BMIPP scintigraphy in patients is performed under resting and fasting conditions.

### BMIPP in ischemia and viability

The initial clinical studies with BMIPP by Dudczack et al.<sup>33</sup> using planar imaging, confirmed the expected prolonged myocardial retention, providing excellent delineation of the myocardium. Considering the advantages of tomography, more recent BMIPP studies have exclusively used SPECT.

For the detection of ischemia and viability, BMIPP is used often in conjunction with a perfusion tracer (thallium-201, technetium-99m sestamibi). In segments with reduced resting perfusion, BMIPP uptake can be concordantly reduced (perfusion-BMIPP match),

more severely reduced (perfusion-BMIPP mismatch) or relatively increased (reversed perfusion-BMIPP mismatch).

Matsunari et al.<sup>34</sup> reported that areas with a perfusion-BMIPP mismatch exhibited redistribution on stress-redistribution thallium-201 imaging (indicating ischemically jeopardized viable tissue). Franken et al.<sup>35</sup> demonstrated that patients with a recent myocardial infarction showed preserved contractile reserve during low-dose dobutamine echocardiography in regions with a perfusion-BMIPP mismatch, again indicating the presence of viable myocardium in these regions. Conversely, none of the regions with a perfusion-BMIPP match exhibited contractile reserve, suggesting that these regions represented scar tissue.

Subsequently, studies evaluated whether BMIPP SPECT could predict recovery of LV function following reperfusion in acute myocardial infarction.<sup>36,37</sup> LV function improved significantly in the patients showing a perfusion-BMIPP mismatch during the acute stage; in contrast, no change in LV function was noted in the patients with a perfusion-BMIPP match. Moreover, the extent of mismatch was closely related to the extent of recovery at follow-up.

There are only a few studies to determine whether BMIPP imaging is also useful to differentiate viable myocardium from scar tissue

in patients with chronic coronary artery disease and LV dysfunction. Two studies evaluated patients with chronic coronary artery disease and LV dysfunction who underwent revascularization.<sup>38,39</sup> Taki et al.<sup>39</sup> evaluated patients with chronic coronary artery disease with BMIPP and resting thallium-201 (to assess perfusion) prior to revascularization: wall motion was assessed before and after revascularization. Improvement of function occurred in 17 of 20 regions with a perfusion-BMIPP mismatch, compared with 1 of 4 regions with a perfusion-BMIPP match. Accordingly, a sensitivity of 94% and a specificity of 50% to predict improvement of regional function after revascularization were obtained (Figure 2).

Prediction of improvement of global LV function after revascularization was also evaluated by Taki et al.<sup>39</sup> Six out of 10 patients who were classified viable by BMIPP imaging improved in LVEF, whereas 6 of 9 patients who were classified as **nonviable** did not improve in LVEF. Similar data were shown by Hambije et al.<sup>38</sup> Pooling the data from these two studies yielded a sensitivity of 81% and a specificity of 56% to predict improvement of LVEF after revascularization (Figure 2). In addition, Hambije et al.<sup>38</sup> demonstrated that in patients who continued to show an area of mismatch 6 months after revascularization, a further increase in LVEF could be anticipated at 1-year follow-up.

Finally, Tamaki et al.<sup>40</sup> evaluated the prognostic significance of areas showing a perfusion-BMIPP mismatch in a cohort of 50 patients with chronic coronary artery disease, with a mean follow-up of 23 months. Nine patients experienced a cardiac event during the follow-up period, including two cases of **nonfatal** infarction, five cases of unstable angina and two cases of late revascularization. Univariate analysis showed that the number of segments with a perfusion-BMIPP mismatch was the best predictor of future cardiac events.

Thus, most of the currently available literature indicates that myocardium showing a reduction in perfusion with a further reduction in BMIPP uptake (mismatch pattern) indicates jeopardized but viable tissue that may

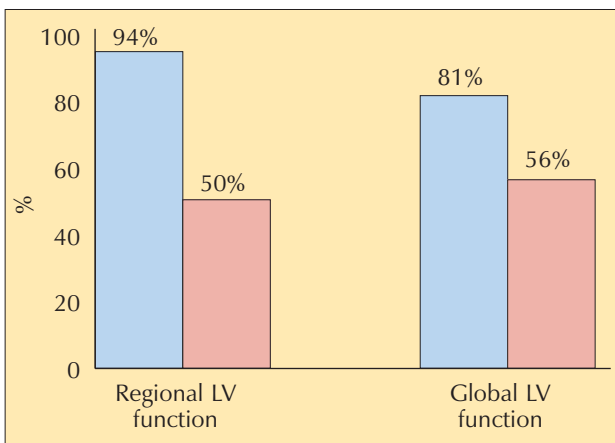


Figure 2. Bar graph demonstrating the sensitivity (blue bars) and specificity (red bars) of BMIPP SPECT for the prediction of improvement of regional and global LV function post-revascularization (based on references 38 and 39).

recover spontaneously (in acute myocardial infarction) or after revascularization (in chronic coronary artery disease), whereas myocardium exhibiting a concordantly reduced perfusion and BMIPP uptake is likely to represent scar tissue that does not have the potential for recovery of function. Besides the matches and mismatches, a reverse mismatch pattern (BMIPP uptake increased relative to perfusion) has been noted. While this pattern is relatively scarce in patients with acute myocardial infarction, it has been observed more often in patients with chronic coronary artery disease. Sloof et al.<sup>41</sup> recently compared BMIPP and FDG imaging in patients with chronic coronary artery disease and LV dysfunction. The authors demonstrated that segments with a reversed perfusion-BMIPP mismatch frequently exhibited a perfusion-FDG mismatch (see below), suggesting the presence of viable tissue. Unfortunately, the patients did not undergo revascularization and therefore functional outcome after revascularization could not be assessed. Thus, the exact relevance of reverse mismatches remains unclear and awaits further study.

### Assessment of glucose metabolism: <sup>18</sup>F-fluorodeoxyglucose (FDG)

#### FDG as a tracer

FDG is a glucose analogue (one OH group has been replaced by F18) and the initial trans-sarcolemmal uptake of FDG is identical to that of glucose. FDG competes with glucose for uptake and phosphorylation to FDG-6-PO<sub>4</sub>, a process mediated by the enzyme hexokinase. Unlike glucose-6-PO<sub>4</sub>, FDG-6-PO<sub>4</sub> does not undergo further metabolism and remains trapped in the myocyte. FDG uptake in the myocardium is highly dependent on the presence of competing substrates (free fatty acid, lactate, amino acids) and hormonal plasma levels (mainly insulin). Since low free fatty acid levels and high glucose/insulin levels promote FDG uptake, cardiac FDG studies are preferably performed following oral glucose loading. To further standardize the metabolic

circumstances, hyperinsulinemic-euglycemic clamping has been advocated.<sup>42</sup> Although this approach results in superb image quality (even in patients with diabetes mellitus), the procedure is rather laborious and time-consuming. Recently, the use of nicotinic acid derivatives (acipimox) has been suggested and the initial results are promising.<sup>43,44</sup> Oral administration of these substances results in extremely low plasma free fatty acid levels, and when administered in combination with a small meal (to stimulate endogenous insulin production) the image quality of cardiac FDG studies was comparable to that obtained following hyperinsulinemic-euglycemic clamping.<sup>43,44</sup>

#### FDG in ischemia and viability

As in BMIPP studies, FDG imaging is usually combined with perfusion imaging. Similar to the BMIPP studies, different perfusion-FDG patterns can be observed: viability on perfusion-FDG imaging is defined when either perfusion is normal (consistent with [repetitive] stunning) or when increased FDG uptake is present in perfusion defects (perfusion-FDG mismatch, probably reflecting hibernation). Scar tissue is characterized by a concordant reduction in perfusion and FDG uptake (perfusion-FDG match).

Since FDG is a **positron-emitter**, FDG imaging is traditionally performed using PET equipment. However, due to the relatively long half-life of F18 (110 min) on the one hand, and to the development of 511 keV collimators on the other, FDG imaging is also feasible with SPECT. Over the past 5 years, substantial experience with cardiac FDG SPECT imaging has been obtained.<sup>45</sup> Although resolution of SPECT is inferior to that of PET, similar clinical information (perfusion-FDG mismatches and matches) can be derived from FDG SPECT as with FDG PET. An example of FDG SPECT showing a perfusion-FDG mismatch is given in *Figure 3*.

Several studies have directly compared FDG PET with FDG SPECT, and were consistent in demonstrating a good agreement between PET and SPECT in the assessment of viable

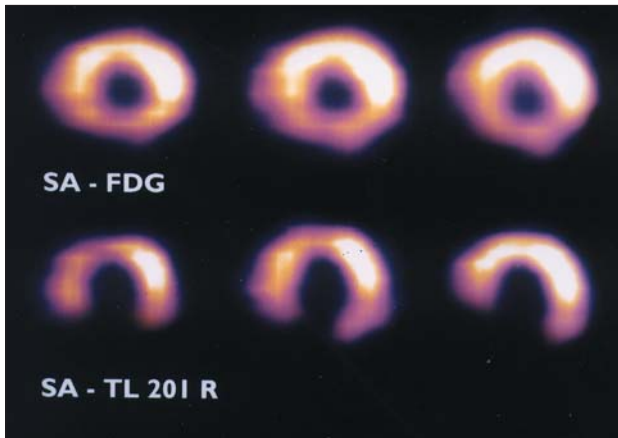


Figure 3. Two series of short-axis slices of a patient with a perfusion-FDG mismatch; in the inferior wall, perfusion (assessed by resting thallium-201, lower series) is absent, whereas FDG uptake (upper series) is relatively preserved. (Reproduced from reference 54 with permission.)

myocardium. For example, Burt et al.<sup>46</sup> studied 20 patients with chronic coronary artery disease; all of these patients had a defect on 4-h delayed resting thallium-201 imaging. Subsequently, these patients underwent both FDG PET and FDG SPECT. Sixty-one segments exhibited a defect on thallium-201 imaging, 11 segments showed preserved FDG uptake on both PET and SPECT, and 45 showed absent FDG uptake on both PET and SPECT. Accordingly, similar information concerning viability/scar tissue was provided in 56 of 61 (92%) segments. Hence, the available data indicate that FDG imaging with PET and SPECT provide similar information considering tissue classification.

Over the past 15 to 20 years, numerous studies have used FDG imaging to evaluate the presence of residual glucose utilization in patients with acute ischemic syndromes and in patients with chronic coronary artery disease and LV dysfunction.<sup>27</sup> Most clinical experience, however, has been obtained in patients with chronic ischemic LV dysfunction. In these patients, FDG imaging, combined with perfusion imaging, can detect residual viable tissue and predict improvement of LV function after revascularization. Recently, the results of 12 FDG PET studies were pooled to determine the value of FDG PET for the prediction of improvement of regional LV func-

tion after revascularization.<sup>27</sup> Pooling of the results yielded a sensitivity of 88% with a specificity of 73%. Studies using FDG SPECT demonstrated similar results: Bax et al. evaluated 55 patients with severe coronary artery disease and depressed LV function (LVEF  $39 \pm 14\%$ ) with SPECT prior to revascularization.<sup>47</sup> Recovery of function was observed in 94 segments, of which 80 were classified viable on FDG SPECT. Alternatively, 187 segments did not improve in function and 141 of these were classified non-viable by FDG SPECT. Thus, a sensitivity of 85% and a specificity of 75% to predict improvement of regional LV function were derived.

Although the prediction of improvement of regional LV function is important, the prediction of improvement of global LV function is probably more relevant from a clinical point of view, since LVEF is an important prognostic parameter. Several FDG PET studies have demonstrated that patients with viable tissue are likely to improve in LVEF, in contrast to patients without viable tissue.<sup>48</sup> In fact, 11 studies have evaluated LVEF before and after revascularization and related the findings to the FDG PET data. In 10 of 11 studies, the average LVEF improved significantly in patients with viable tissue on FDG PET (ranging from 7% to 18% absolute increase in LVEF). In seven of these studies 'non-viable patients' (according to the PET findings) were also included; none of these studies demon-

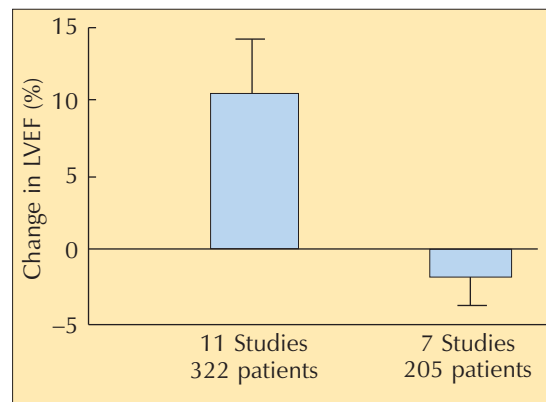


Figure 4. Average changes in LVEF following revascularization in studies with 'FDG PET viable' patients (left) and 'FDG PET non-viable' patients (right) (based on references 48).

strated an improvement in average LVEF (from 4% absolute increase to 12% absolute decrease in LVEF). The average LVEF improved by  $10.6 \pm 4.1\%$  in the studies with viable patients and decreased by  $-1.7 \pm 2.1\%$  in the studies with the non-viable patients (Figure 4).

Frequently, the improvement in LVEF is accompanied by an improvement in heart failure symptoms. Bax et al.<sup>49</sup> have recently evaluated 47 patients with ischemic cardiomyopathy (LVEF  $30 \pm 6\%$ ) with FDG SPECT prior to revascularization. The patients were divided into three groups, according to the number of dysfunctional but viable segments on FDG SPECT (using a 13-segment model). Group I consisted of 22 patients without substantial viability (<3 viable segments), group II consisted of 17 patients with an intermediate amount of viable tissue (3–5 segments) and group III consisted of eight patients with a large amount of viable tissue (>5 segments). In group I, heart failure symptoms (expressed in NYHA scores) did not change. In group II, a modest improvement in heart failure symptoms was observed, but the largest improvement NYHA score was observed in group III (Figure 5).

Two FDG PET studies have also evaluated the change of symptoms and exercise capacity

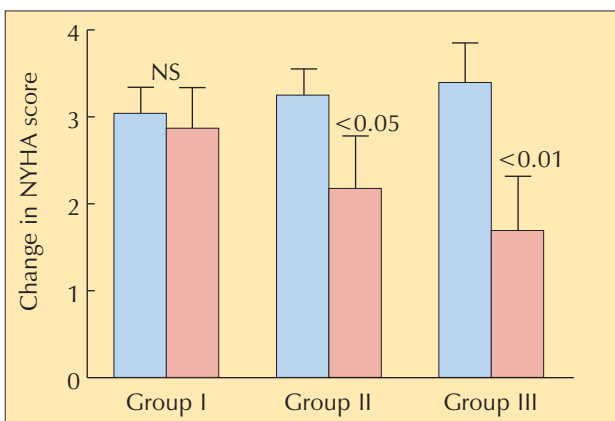


Figure 5. Changes in heart failure symptoms (scored according to the NYHA classification) following revascularization in three groups of patients. Blue bars represent NYHA score before revascularization, red bars represent NYHA score after revascularization (based on reference 49).

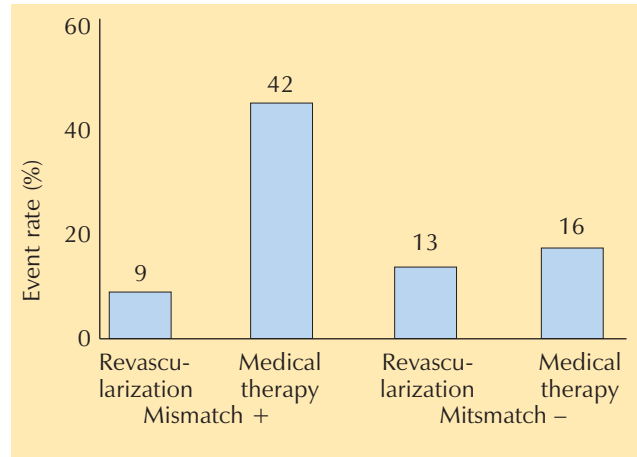


Figure 6. Pooled data from five FDG PET studies (549 patients) evaluating the prognostic value of the technique. The bars represent the event rate according to the treatment (revascularization or medical therapy) and the absence (mismatch -) or presence (mismatch +) of viable tissue on FDG PET. The highest event rate was observed in the viable patients who were treated medically (based on reference 52).

in viable and non-viable patients.<sup>50,51</sup> Marwick et al.<sup>50</sup> evaluated patients with FDG PET, prior to revascularization. The results indicated that patients with substantial viability demonstrated a significant improvement in exercise capacity. Finally, the long-term prognostic value of FDG PET was evaluated in five studies, with a total of 549 patients.<sup>52</sup> These patients were grouped according to treatment (revascularization/medical) and viability status (absent/present) (Figure 6). The mean follow-up varied from 12 to 29 months. The highest event rate (42%) was observed in the viable patients who were treated medically, whereas the lowest event rate (9%) was observed in the viable patients who underwent revascularization (Figure 6).

These results suggest that residual viability in patients with chronic coronary artery disease and depressed LV function is an unstable situation prone to future events. An important limitation of these studies is their retrospective, non-randomized character. Prospective, randomized trials are needed to determine the precise impact of viability in combination with treatment on long-term survival.

## Conclusion

Heart failure secondary to coronary artery disease is becoming one of the major concerns in clinical cardiology. Besides medical therapy and heart transplantation, coronary revascularization can be an alternative treatment. In order to justify the higher risk of revascularization in patients with heart failure, detection of viable myocardium has become an important issue. According to the many studies in the literature, improvement of LV function, heart failure symptoms and prognosis can only be anticipated in patients with substantial viable tissue. Metabolic imaging using PET and SPECT in combination with a variety of radionuclides allows **noninvasive** assessment of the “viability status” of the myocardium, and provides a useful tool to guide patient management.

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# Myocardial viability assessment: how, in which patients, and when?

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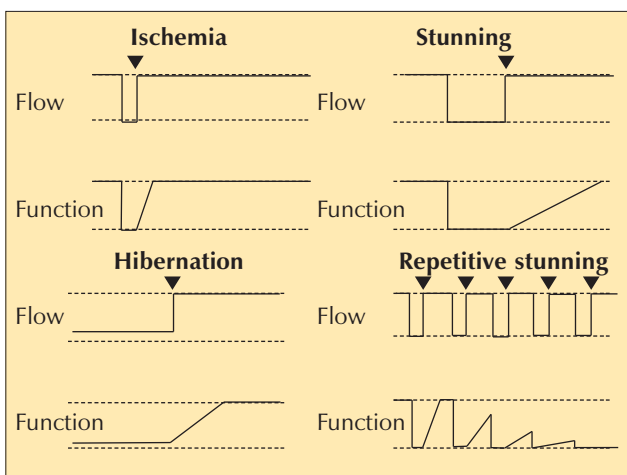
## Introduction

The term “viable myocardium” has been introduced in clinical practice to characterize dysfunctional tissue in patients with coronary artery disease (CAD) that has the potential to recover its function. Contractile dysfunction may be caused by necrotic myocardium or by viable myocardium. If the dysfunction is due to fibrosis, no recovery can be expected; if the dysfunction is due to viable myocardium, recovery can occur in some patients.<sup>1,2</sup>

Reversible dysfunction can be caused by several mechanisms including ischemia, hibernation, stunning and repetitive stunning. *Figure 1* is a schematic representation of the relation between flow and function under these different conditions. During episodes of ischemia function is depressed but returns to normal after disappearance of the ischemia. During prolonged episodes of ischemia followed by reperfusion, which may occur in the

setting of acute myocardial infarction treated by reperfusion therapy, restoration of function may be considerably slower. In hibernating myocardium, function is adapted to a situation of chronic underperfusion. Finally, repetitively stunned myocardium denotes a progressive loss of function after repetitive episodes of ischemia. Although the exact pathophysiology of dysfunctional but viable myocardium is still unclear and remains controversial,<sup>2-4</sup> the potential for functional recovery has clinical relevance. Indeed, whatever the exact mechanism of reversible dysfunction, reperfusion in the acute stage of ischemic syndromes or revascularization in the chronic stage is required for functional recovery.

The awareness that even severely dysfunctional myocardium in patients with CAD may show an improvement in functional state after revascularization has resulted in a tremendous amount of research to identify viable tissue by the optimal diagnostic approach.



*Figure 1. Schematic representation of the relation between flow and function in different pathophysiological conditions. The arrow indicates restoration of normal flow.*

## How to assess viability

A large number of techniques have been developed to identify dysfunctional but viable myocardium. An in-depth review of available techniques has been discussed in a previous issue of Heart and Metabolism by Senior and Lahiri<sup>5</sup> and in this issue by Bax et al., and include perfusion imaging (nuclear and echocardiography), metabolic imaging (nuclear) and imaging of contractile reserve (echocardiography and magnetic resonance imaging). However, most studied and commonly used in clinical practice are fluorine-18 fluorodeoxyglucose (FDG), thallium-201 (Tl-201) stress-redistribution-reinjection, Tl-201 rest-redistribution, technetium-99m (Tc-99m)

sestamibi (MIBI) single photon emission computed tomography (SPECT) and low-dose dobutamine echocardiography (LDDE). Their relative advantages are outlined below.

### **FDG**

Since the original observation by Marshall et al.<sup>6</sup> in 1983, considerable evidence has accumulated to show that FDG in combination with PET can detect viable myocardium. FDG is a glucose analog that traces exogenous glucose uptake by the myocardium. Viable myocardium is characterized by preserved FDG uptake in an area with depressed left ventricular (LV) function. Many studies have validated the use of FDG for the prediction of functional recovery in patients undergoing revascularization.<sup>7</sup>

### **Tl-201 scintigraphy**

The initial uptake of Tl-201 by myocytes is mainly determined by regional perfusion, whereas the integrity of the cell membrane is predominantly important for delayed imaging of tracer retention. Although different Tl-201 protocols have been described,<sup>8</sup> mainly Tl-201 stress-redistribution-reinjection and Tl-201 rest-redistribution are currently used. Studies have shown<sup>9</sup> that after reinjection of 1 mCi of Tl-201 after 3–4 h redistribution imaging detects viability in more than one third of segments deemed irreversibly damaged because they showed a fixed defect on conventional stress-redistribution Tl-201 imaging. The ability to detect viable myocardium was demonstrated by several studies in which viability was compared with functional outcome after revascularization.

Whereas Tl-201 stress-redistribution-reinjection scintigraphy provides information on both exercise-induced ischemia and viability, Tl-201 rest-redistribution provides information on viability only. A large number of studies have evaluated the use of Tl-201 rest-redistribution imaging in revascularized patients. Two studies<sup>10,11</sup> compared Tl-201

stress-redistribution-reinjection with Tl-201 rest-redistribution imaging and showed a concordance between the two techniques of 80%, at least when defect reversibility was considered an indicator of viability. When the severity of Tl-201 activity in irreversible defects was taken into account, the concordance increased to 94%.<sup>10</sup>

### **Tc-99m MIBI**

Myocardial uptake of Tc-99m MIBI parallels regional perfusion and provides adequate information for the detection of CAD. The uptake and retention of Tc-99m MIBI is also dependent on cell membrane integrity and mitochondrial function (membrane potential)<sup>12,13</sup> and thus may reflect cellular viability. Many studies have compared Tc-99m MIBI imaging with other scintigraphic modalities, including Tl-201 stress-redistribution-reinjection,<sup>14</sup> Tl-201 rest-redistribution<sup>15</sup> and FDG PET.<sup>16</sup> These concordance studies were consistent in showing that Tc-99m MIBI was less accurate in the detection of myocardial viability. However, specificity of Tc-99m MIBI is higher than that of Tl-201 stress-redistribution-reinjection and Tl-201 rest-redistribution in detecting absence of functional recovery after revascularization.

### **Low-dose dobutamine echocardiography**

Echocardiography during the infusion of low dose dobutamine (5–15 µg/kg body weight per min) has been proposed as an alternative method for assessing myocardial viability in patients with chronic ischemic heart disease.<sup>17</sup> The hallmark of viability is improved contraction of a dysfunctional segment after adrenergic stimulation. Available studies indicate that LDDE<sup>7</sup> adequately detects recovery of contractile function after revascularization. Several studies have compared LDDE with other imaging modalities to assess viability, including FDG PET,<sup>18</sup> Tl-201 stress-redistribution-reinjection,<sup>19</sup> Tl-201 rest-redistribution<sup>20</sup> and Tc-99m MIBI,<sup>21</sup> showing good agreement in most studies.

### Which technique to choose

Bax et al. performed a meta-analysis on the diagnostic value of the five above-mentioned, most clinically used techniques<sup>7</sup> to assess viability. In this meta-analysis the data publications were reanalyzed and the sensitivity and specificity plus the 95% confidence intervals of the techniques to predict presence and absence of recovery of regional function after revascularization were calculated. Recovery of function is considered to be the gold standard for assessing viability. The results, as previously published<sup>7</sup> and discussed in *Heart and Metabolism* by Senior and Lahiri<sup>5</sup> (Figure 2), showed that Tl-201 reinjection and Tl-201 rest-redistribution had a high sensitivity (90% and 86%, respectively) but a low specificity of 47% and 54%, respectively. Tc-99m MIBI had an intermediate specificity of 69%. LDDE had the highest specificity of 81%, but the sensitivity of FDG PET was higher (88%) than that of LDDE (84%).

Do these results imply that Tl-201 techniques should not be used to assess viability?

Although the specificity of Tl-201 reinjection and rest-redistribution were lower compared to the other techniques, the question is how clinically relevant this low specificity is. Because of the high sensitivities, the negative predictive value for functional outcome is high (assuming a balanced division between recoverable and non-recoverable regions in the study population). Thus, patients are probably correctly deferred from revascularization if no viable tissue is present and the cardiologist/ cardiac surgeon may take the risk of absence of functional recovery because patients are usually proposed for revascularization because of angina.

In this respect it is worthwhile noting that the prevalence of recoverable segments after revascularization varied greatly between studies, ranging between 22% and 82%. This suggests major differences between populations studied.

Moreover, we have recently studied the diagnostic value of rest-redistribution Tl-201 SPECT for the prediction of global LV functional recovery after revascularization. The

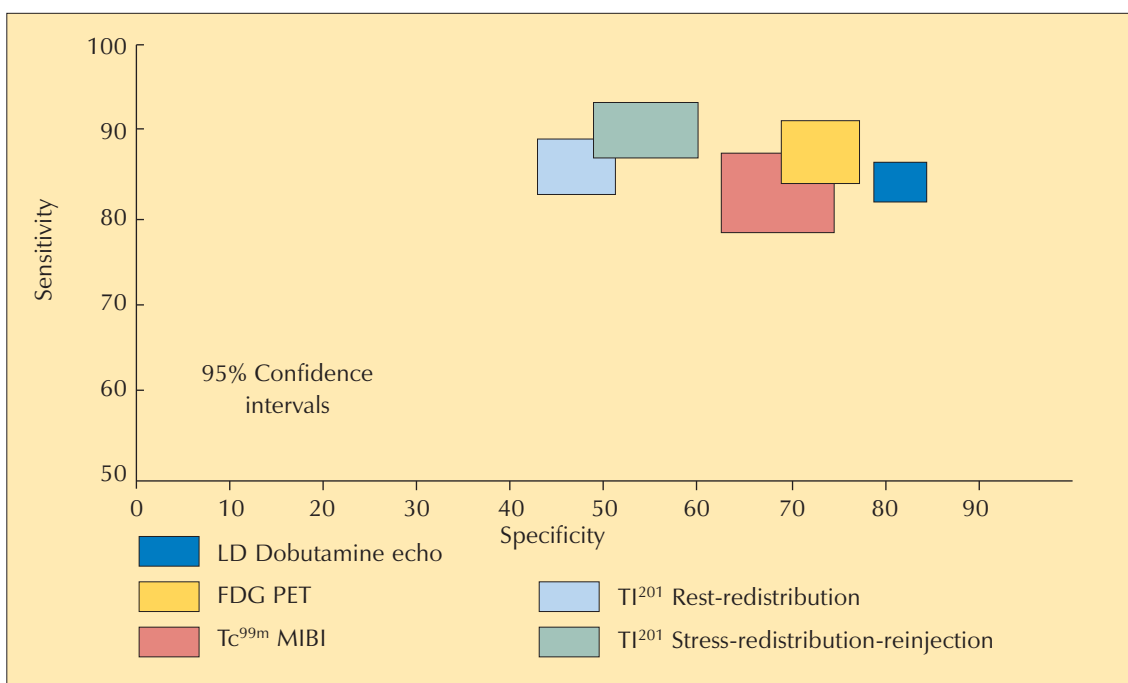


Figure 2. Sensitivity and specificity of LDDE, FDG PET, Tc-99m MIBI, Tl-201 rest-redistribution and of Tl-201 stress-redistribution-reinjection to predict functional recovery after revascularization. The lines of the boxes represent the 95% confidence intervals of the sensitivity and specificity of the techniques. (With permission of the J Am Coll Cardiol.)<sup>7</sup>

specificity for detecting absence of global functional improvement (defined as an improvement of at least 5 ejection fraction units) was 76%.<sup>22</sup> This implies that the TI-201 techniques are adequate for the more clinically relevant global functional improvement after revascularization. Also, the presence of viable myocardium may have implications for, and may have long-term effects on, clinical factors that are independent from the resting functional state of the left ventricle. These factors include prognosis<sup>23</sup> (see below), the response during stress,<sup>24</sup> exercise capacity<sup>25</sup> and quality of life.<sup>26</sup> At present, the relative merits of the different viability techniques for the prediction of these clinical factors are largely unknown and should be prospectively evaluated in a large patient cohort.

Moreover, the meta-analysis of the published data revealed some of the weaknesses of the currently available evidence. The inclusion criteria varied considerably between studies, particularly with respect to the severity of baseline dysfunction. Ideally, only patients with a global ejection fraction <30–35% should be studied because these patients are likely both to benefit from and to have a greater risk during revascularization. Most studies included only a limited number of patients, suggesting inclusion bias. The majority of studies did not provide evidence of vessel or graft patency; reocclusion may prohibit viable segments from recovering, thereby underestimating the true specificity of all techniques. The optimal moment for the assessment of functional follow-up after revascularization is uncertain. Currently, follow-up is frequently performed 3 months after revascularization. However, preliminary data have demonstrated that full recovery is not expected to occur before 6 or even 12 months after revascularization. Importantly, global and regional function should be evaluated by an independent technique. Studies of LDDE have invariably used echocardiograms to evaluate the effect of revascularization. The use of an internally consistent standard may contribute in part to the excellent diagnostic value of this technique. In addition, the acquisition and interpretation of echocardiograms strongly

depends on operator experience.

Thus, in practice, the choice between imaging modalities also depends on local availability, the status of the equipment, the waiting list, the prevalence of viable/non-viable tissue in the local population (largely influencing predictive values of functional improvement) and expertise in acquisition and interpretation, which is particularly critical for LDDE.

Finally, it is obvious that the viability tests are not perfect and have different performance characteristics. Possibly, complementary techniques should be combined to obtain the best clinical prediction. Then strategies can be developed for a cost-effective use of tests in a sequential manner, as preliminary data suggest.<sup>27</sup>

### Clinical value of viability testing

Viability detection can be used to clarify a number of clinical issues: 1) pre-operative detection of functional recovery after revascularization in patients with chronically depressed LV function, 2) determination of prognosis in patients with chronic CAD, 3) peri-operative risk assessment in patients undergoing revascularization, 4) prediction of reversal of LV dysfunction after acute myocardial infarction, and 5) determination of prognosis after myocardial infarction.

### *Pre-operative detection of functional recovery after revascularization in patients with chronically depressed LV function*

As discussed above and in this issue a large number of studies have been published showing that viable tissue is related to improvement of regional and global LV function after revascularization. Moreover, improvement of function is associated with improvement of heart failure symptoms and exercise capacity. Reversal of myocardial dysfunction is particularly relevant in patients with depressed ventricular function because surgical revascularization improves long-term survival in such patients.<sup>28</sup>

### ***Determination of prognosis in patients with chronic CAD***

In addition to the prediction of functional recovery after revascularization, viability imaging may also provide prognostic information on morbidity and mortality. In this issue Bax et al. show the data of FDG PET studies, indicating that the presence of viability in patients who are treated medically is associated with a high event rate, much higher than in patients with viable tissue who underwent revascularization, or in patients without viable tissue, independent of the revascularization. These findings have been confirmed by other techniques. Recently, similar results were published with TI-201 rest-redistribution imaging. Gioia et al.<sup>29</sup> studied the prognosis of patients with severe LV dysfunction, who were treated medically. During a mean follow-up of 31 months, there were 11 cardiac deaths in patients with no redistribution (26%) on TI-201 rest-redistribution imaging and 22 in patients with redistribution (58%), and multivariate Cox survival analysis on important clinical, angiographic and thallium variables showed that the presence of viability was an independent predictor of death. Meluzin et al.<sup>30</sup> divided revascularization patients into three groups: based on LDDE studies. Patients with extensive viable tissue had the lowest event rate, confirming previous findings.

### ***Peri-operative risk assessment in patients undergoing revascularization***

Not only is viability assessment useful for the long-term outcome after revascularization, but may also be used for perioperative risk assessment. Haas et al.<sup>31</sup> studied 76 patients with advanced CAD and poor LV function who underwent CABG. Of these patients 35 underwent CABG on the basis of clinical and angiographic data, while 41 also underwent FDG PET imaging. Patients without viability assessment had a significantly higher mortality (11%) compared with patients with viability assessment (0%). Postoperatively, viability-tested patients had a less complicated recovery.

They required lower doses of catecholamines and demonstrated a significantly decreased incidence of low output syndrome. Although this was a retrospective study in which the reasons for performing FDG PET, the presence of viable tissue and the decision process for accepting patients are not given, the data suggest that, if cardiac surgeons include viability data in their patient management, peri- and postoperative outcome may be better than without the use of viability data. Larger, prospective studies are needed to confirm these findings.

### ***Prediction of reversal of LV function after acute myocardial infarction***

The presence of viability in patients with an acute myocardial infarction is associated with improvement of LV function during follow-up. Schwaiger et al. performed in 1986 a study in which patients underwent FDG imaging early after myocardial infarction.<sup>32</sup> They found that viable segments showed improvement of regional function during follow-up in 50%, in contrast to non-viable segments, which showed no improvement at all. These FDG findings were confirmed by Huitink et al.<sup>33</sup> Also, LDDE has been successfully employed to predict functional recovery after acute myocardial infarction.<sup>33–37</sup> Thus, viability in the infarct area is associated with spontaneous improvement of LV function and the absence of viability is strongly predictive of absence of recovery.

### ***Determination of prognosis after myocardial infarction***

Data regarding the effect of viability on prognosis after acute myocardial infarction are conflicting: some studies associated viability with a poor prognosis and some with a good prognosis.

Brown et al.<sup>38</sup> found that patients with viability had a higher risk of cardiac events. Similarly, Basu et al.<sup>39</sup> found in infarct patients treated with thrombolysis that the event-free

survival of patients with reversible perfusion defects, detected by stress/nitroglycerine-enhanced rest Tl-201 imaging was significantly lower than in patients without reversible perfusion defects. Strikingly, Tl-201 stress-redistribution imaging (without the use of nitroglycerine) did not discriminate between event and event-free patients. At our institution two prognosis studies in patients admitted with an acute myocardial infarction were performed. Huitink et al.<sup>40</sup> performed planar FDG imaging and followed the infarct patients for a mean of 47 months (Figure 3). Patients with viable tissue had a 49% event rate, in contrast to 7% in patients without viability;  $p < 0.009$ . Nijland et al.<sup>41</sup> studied the in-hospital event rate of admitted patients. Viability was assessed by LDDE early after infarction. They found in patients with viability an in-hospital event rate of 32% versus 10% in patients without viability;  $p < 0.05$ . Thus, these data on patients with acute MI are in line with prognosis data in patients with chronic CAD (see above).

The small study by Yoshida and Gould using PET<sup>42</sup> and, especially, the study by Carlos et al.<sup>43</sup> using LDDE showed that viability, together with a small infarct size and absence of ischemia, was associated with a good prognosis after myocardial infarction (Figure 4).

Also, Picano et al.<sup>44</sup> found in medically treated patients that the presence of viable tissue exerted a protective effect after infarction

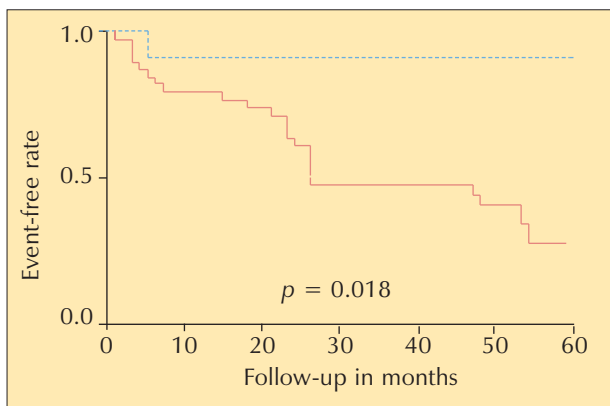


Figure 3. Viability and poor prognosis after myocardial infarction. Patients with viable tissue (solid line) had a significantly higher event rate than patients without viable tissue (dashed line). (With permission of the Am J Cardiol.)<sup>40</sup>

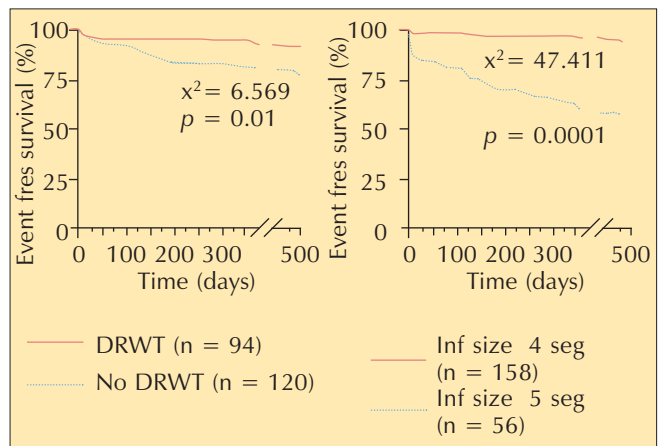


Figure 4. Viability and good prognosis after infarction. Patients with viable tissue as assessed by dobutamine regional wall thickening (DRWT) had a significantly lower event rate than patients without DRWT. Similarly, patients with a small infarct size (Inf Size) had a better event free survival. (With permission of Circulation).<sup>43</sup>

by reducing death. Finally, Previtali et al.<sup>45</sup> also combined viability and ischemia detection in infarction patients. The combination of viability and ischemia had the highest hard and soft event rate after infarction, but multivariate analysis showed that the presence of ischemia was the most important predictor of events, while viability had no prognostic value.

Thus, the data on the prognostic value of viability after infarction are conflicting. Prognosis after acute infarction depends on a large number of factors, including the site of infarction, extent of infarction/degree of LV dysfunction, extent of coronary artery disease and ischemia in and outside the infarction area, the choice of treatment in the acute phase and thereafter (medical, thrombolysis, PTCA) and many other clinical factors which have to be unaccounted for. All these factors may have a complicated interaction obscuring the contribution of one single parameter. Therefore, to assess the prognostic value of viability, randomized clinical trial are needed, comparing standard treatment of viability after infarction with PTCA of the infarct-related coronary artery. This trial is being setup in the Netherlands.

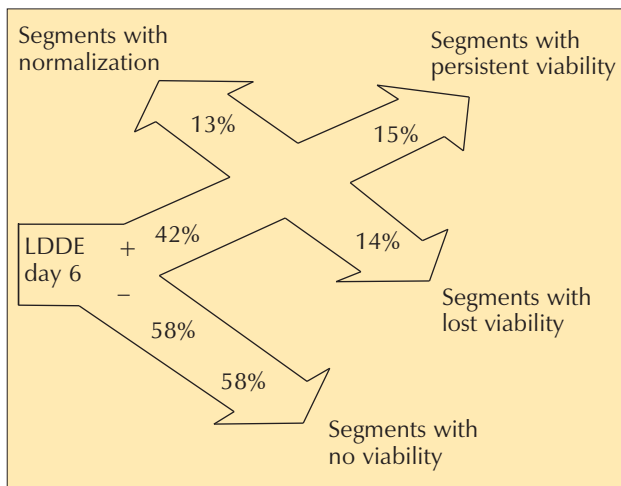


Figure 5. Time-course of viable tissue (LDDE +) in patients after infarction. In one third of patients with viable tissue, viability was lost during follow-up. (With permission of the Am Heart J.)<sup>46</sup>

### When to assess viability

Using LDDE and PET, Pierard et al.<sup>34</sup> studied patients with acute anterior infarction, treated with thrombolysis. Functional recovery during follow-up was observed in all patients with normal perfusion and LDDE, viable segments. In patients with increased FDG uptake and contractile recovery during LDDE recovery of function during follow-up was observed in a minority of patients, whereas patients without signs of viability with either technique showed no recovery. These data were confirmed by Knudsen et al.<sup>46</sup>: see Figure 5. Using LDDE, they found that one third of viable tissue early after infarction lost the ability to respond to dobutamine during follow-up, suggesting loss of viability in the time-course after infarction. In the study of Pierard et al.<sup>34</sup> this tissue was characterized by an increased FDG uptake, suggesting jeopardized myocardium that frequently loses viability in the absence of revascularization. Indeed, Barilla et al.<sup>35</sup> demonstrated that acute infarct patients with viable tissue who underwent coronary revascularization showed a better LV functional improvement during follow-up than infarct patients with viable tissue who were treated medically.

Similar findings were observed in patients

with chronic LV dysfunction: Schwartz et al.<sup>47</sup> estimated the duration of viable tissue before revascularization and found that only in patients with viability of a short-time duration LV function improved after revascularization. Beanlands et al.<sup>48</sup> studied the duration of the waiting list and observed a significantly better improvement of LV function after revascularization in patients on a short waiting list. These data suggest that viable areas are at risk of deterioration. Probably, these patients merit early revascularization for improvement of LV function and thus prognosis.

### Which patients need viability testing

Based on the data presented above, viability testing is recommended in patients with chronic left ventricular dysfunction due to coronary artery disease. If extensive viable tissue is present, improvement of LV function, symptoms, exercise capacity, quality of life and prognosis is to be expected after revascularization. In clinical practice, however, a considerable number of these patients also have anginal complaints due to (exercise-induced) ischemia. If these patients are accepted for total revascularization (CABG), viability assessment may not be necessary because revascularization is performed both on vessels causing ischemia and on vessels causing chronic dysfunction. When in these anginal patients there is doubt about grafting an artery (e.g. after chronic infarction), then additional viability assessment needs to be performed. Finally, the cardiac surgeon may want viability assessment for peri-operative risk stratification. Nevertheless, a weakness of the above mentioned data in chronic CAD is that most of the studies on improvement of function and prognosis were retrospective in nature, possibly leading to patient bias. For example, improvement of function could only be assessed in patients who survived follow-up after revascularization. Also, major improvements in medical treatment have been obtained in the last decade by the standard treatment of heart failure with ACE-inhibitors and beta-blockers. Addition of beta-blockers on top of ACE-

inhibitors and diuretics has been shown to improve both survival and left ventricular function. A meta-analysis of the available data on the effects of beta-blockers on left ventricular function showed that on average the ejection fraction rose more than 6%,<sup>49</sup> irrespective of the presence or absence of viable tissue in these patients! Therefore, a randomized trial is needed to show that revascularization of viable tissue is superior to optimal medical treatment in patients with chronic LV dysfunction and mild or no angina.

Another important group of patients are those in whom a choice has to be made between revascularization and cardiac transplantation. In these patients viability assessment should be an integral part of the diagnostic work-up, because of the potential improvement of function and prognosis of viable tissue as indicated above.

In patients after acute myocardial infarction, recommendations regarding routine assessment of viable tissue are less clear. Stunned myocardium may spontaneously improve over time, giving the cardiologist the opportunity for watchful waiting. On the other hand, initial studies in small numbers of patients suggest that viable tissue may deteriorate over time. Furthermore, data on the impact of viability on prognosis after infarction are conflicting as some of studies associate viability with a good prognosis and some with a poor prognosis. Therefore, further studies giving insight into which patient is at risk after infarction are clearly needed as well as a randomized revascularization trial of viable tissue.

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# Ischemic cardiomyopathy: therapeutic value of a metabolic approach

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Heart failure is a major cause of morbidity and mortality worldwide.<sup>1-3</sup> Indeed, congestive heart failure (CHF) affects between 1 and 4% of the total population.<sup>4,5</sup> Despite many advances in the management of heart failure and coronary heart disease (CHD), which represents the major cause of CHF, the prevalence and incidence of left ventricular dysfunction are increasing dramatically leading to a heavy burden on healthcare systems.<sup>6,7</sup> The increasing prevalence of CHF is the consequence of the aging of the population, the increasing prevalence of CHD, and the reduced age-adjusted mortality of patients with CHD. Better knowledge of the mechanisms which lead to cardiac diastolic or systolic dysfunction has also highlighted the need for reevaluation of the relationship between heart failure and ischemic heart disease (IHD), especially in terms of potential therapeutic improvements.

Ischemic heart disease represents the leading cause of mortality worldwide today. This disease is expected to become the world's primary cause of disease burden (which represents aggregate mortality and morbidity) in 2020, despite considerable progress in prevention and treatment over the past 20 years. IHD is currently the main cause of heart failure, which remains an increasing major clinical and health problem. CHF is associated with poor functional capacity, decreased quality of life, and increased risk of morbidity and mortality, with a common mortality rate in excess of 40% within 2 years of initial diagnosis.<sup>8-11</sup>

The ischemic cause of CHF increases the risk of death;<sup>12</sup> this enhances the importance of an improved therapeutic approach to ischemic cardiomyopathy.

## Evolution in the understanding of ischemic left ventricular dysfunction

In past decades, it was thought that CHF associated with chronic coronary artery disease (CAD) was irreversible and amenable to early medical treatment with hemodynamic agents, such as ACE inhibitors,  $\beta$ -blockers, spironolactone, diuretics, and digoxin if necessary.

This concept has been proven inaccurate, because of the progress in cardiac imaging techniques, which has shown that ischemic left ventricular dysfunction is not always irreversible. The improved myocardial function in some patients after bypass graft or with dobutamine led Rahimtoola to propose the concept of hibernating myocardium.<sup>13</sup> In patients with chronic CAD, hibernation means that left ventricular function seems chronically impaired but is in fact reversible by reperfusion. Clinical syndromes associated with hibernation include stable and unstable angina, myocardial infarction, and documented left ventricular dysfunction with or without cardiac failure. The hibernating myocardium retains its inotropic responsiveness, in contrast to irreversibly damaged muscle. It can be identified by resting and stress echocardiography, thallium scintigraphy, and positron emission tomography (PET).

The development of PET has permitted better exploration of hibernating myocardium and opened up a new controversial issue (*Figures 1 and 2*). In fact, the initial definition of hibernation implied a myocardial dysfunction due to a significant reduction in coronary blood flow. PET studies, which currently represent the most accurate method of measuring blood flow, have highlighted the evidence that blood flow in hibernating segments is not necessarily reduced to an extent that can account alone for the degree of dysfunction. These findings suggest a metabolic adaptation of

myocardial cells, which has been postulated by recent studies. These studies found that the hibernating myocardium is not metabolically anaerobic after a short time, and that an uncoupling of substrate (glucose and fatty acid) uptake and mechanical function happens.<sup>14</sup> In consequence, the glucose oxidation is reduced, leading to an uncoupling between glycolysis and glucose oxidation which results in deleterious effects. The demonstration of significant reversibility of the degree of left ventricular dysfunction, i.e. hibernation, offers the patients the chance to benefit from revascularization, both symptomatically and prognostically.

Considering the potential gain to be derived from revascularization, there is the temptation to perform such aggressive procedures in all patients with a hibernating left ventricle. However, numerous problems have not yet been resolved. It is not known how much viable myocardium is required for revascularization to confer a clinical benefit, or to what extent the interventional strategies result in sustained symptomatic and functional improvement, as well as prognostic benefits compared with optimal medical management. In fact, the conventional drugs used in congestive heart failure, including ACE inhibitors, diuretics, digitalic glycosides, and vasodilators, improve either symptoms and/or prognosis, but the role of these drugs in the specific field of hibernating myocardium has not been evaluated.

Furthermore, hibernating myocardium is the consequence of a progressive metabolic adaptation, which clearly emphasizes the need for therapeutic metabolic modulation in the patient's favor.

### Therapeutic value of a metabolic approach in left ventricular dysfunction

Some promising experimental and clinical studies have been conducted with trimetazidine (Vastarel 20), the first metabolic agent to be quoted in the European Guidelines,

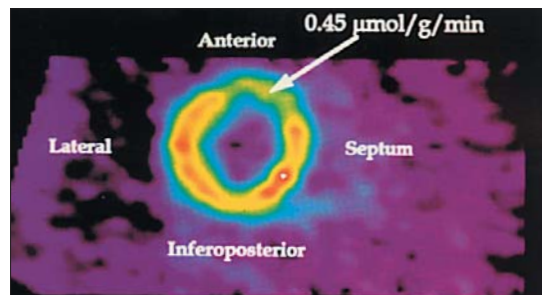


Figure 1. FDG scan from a patient with viable hibernating myocardium.

demonstrating initial promising results in the field of ischemic cardiomyopathy. In fact, this drug has a number of potentially useful cytoprotective features, by limiting intracellular acidosis and sodium and calcium overload, allowing preservation of contractile function and limitation of cytolysis and membrane damage caused by oxygen free radicals.

In animal studies, the original and specific mechanism of trimetazidine causes an increase of 33% in the recovery of cardiac work and a 24% increase in cardiac efficiency in early reperfusion compared with control rat hearts.<sup>15</sup> The clinical studies tend to confirm these benefits: Brottier et al. reported symptomatic and functional improvement, with an increase in left ventricular ejection fraction (EF) in a small cohort of coronary patients with severe left ventricular dysfunction.<sup>16</sup> In 1997, Birand et al. found a significant improvement of EF with trimetazidine, compared with placebo, in 51 patients with CAD after percutaneous transluminal coronary angioplasty (PTCA).<sup>17</sup>

More recently, trimetazidine was found to be effective in improving resting left ventricular function and wall motion score index in a

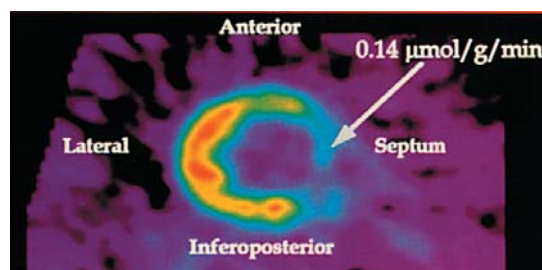


Figure 2. FDG scan from a patient with nonviable scar tissue.

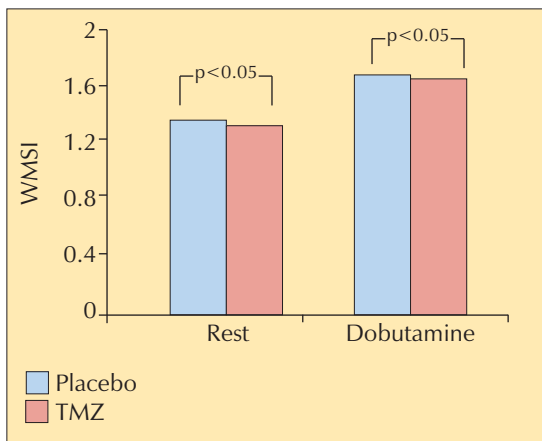


Figure 3. Trimetazidine significantly reduced wall motion score index both at rest and during DET.

randomized, double-blind study, compared with placebo (Figure 3).<sup>18</sup>

A further study has been recently performed to evaluate the activity of trimetazidine in hibernating myocardium (Figures 1 and 2).<sup>19</sup> This double-blind, randomized, placebo-controlled study concluded that there was a significant improvement in wall motion score index both at rest and at peak infusion, without change in the hemodynamic parameters (Figure 4). Improved cellular function during ischemia could explain the beneficial effects of trimetazidine on resting and dobutamine-induced myocardial ischemic dysfunction. Preserving mitochondrial function and energy metabolism from chronic oxygen deprivation may reduce ischemic left ventricular dysfunc-

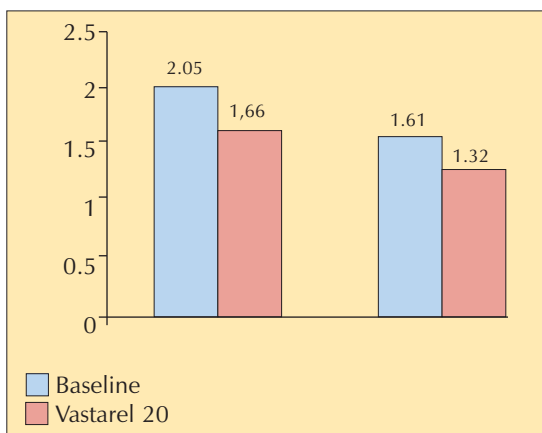


Figure 4. Trimetazidine decreases WMSI at rest and at stress in patients with hibernating myocardium.

tion. As these effects occur in the absence of detectable changes in systemic and coronary hemodynamics, the effects of trimetazidine on ischemic myocardium are likely to rely on direct cytoprotection.

## CONCLUSION

Hibernation is a form of prolonged contractile dysfunction associated with ongoing blood flow in patients with CAD. This newly discovered phenomenon concept is often present in ischemic cardiomyopathy, the main cause of CHF. Stress echocardiography and myocardial tomoscintigraphy represent the most accurate techniques to assess myocardial viability in case of ischemic cardiomyopathy. Trimetazidine, a new metabolic antiischemic agent, has triggered initial promising results in this area.

Further studies are needed for a better understanding of the hibernating myocardium, to evaluate and compare the benefit of anti-ischemic agents in this spectrum, in order to improve the morbidity and the mortality of numerous patients with ischemic CHF.

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# Discordant viability techniques

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## Introduction

Previous studies have demonstrated that myocardial dysfunction characterized by an absence of wall thickening is not necessarily caused by scar tissue, as it can also occur in viable myocardium in instances of stunning or hibernation. The term “stunned myocardium” refers to a reversible form of contractile dysfunction that occurs after restoration of coronary blood flow, following a period of transient ischemia.<sup>1</sup> The duration of stunning can vary between hours and weeks, but its resolution is spontaneous without the need for treatment.

Hibernation describes a state of decreased function caused by an acute (short-term hibernation) or chronic (long-term hibernation) reduction of myocardial blood flow. By definition, the contractility of hibernating myocardium returns after successful revascularization.<sup>2</sup> The concept of short-term hibernation is based on the hypothesis that the metabolic demand of ischemic cells can adapt to the reduced perfusion, establishing a new level of “perfusion-contraction matching” which prevents myocytes from necrosis.<sup>3</sup> Long-term hibernation is also associated with ultrastructural changes such as disorganization and reduction of the myofibrils, and an increase in extracellular collagen and myocardial glycogen content, which may limit or delay functional recovery after revascularization.<sup>4,5</sup>

## Identification of viable myocardium

The identification of viable myocardium is an important clinical task. In patients with severely impaired left ventricular function, surgical intervention is associated with a higher risk of

perioperative complications. Selecting patients with severely depressed myocardial function for revascularization therapy on the basis of prior viability detection significantly lowers the rate of perioperative complications. Furthermore it enables prediction of functional recovery and therefore suggests decreased long-term mortality.<sup>6,7</sup> Thus, major efforts have been made to develop noninvasive methods for detecting viable myocardium.

The information required to assess viability varies between the methods used, but includes measurement of cell metabolism, cell membrane integrity, mitochondrial function and contractile reserve under  $\beta$ -adrenergic stimulation.

## Myocardial energy metabolism assessed by PET

Cardiac myocytes metabolize a wide variety of substrates. Under normoxic conditions, the heart preferentially metabolizes free fatty acids. Their oxidation accounts for about 60% to 70% of total myocardial oxygen consumption in the fasting state.<sup>8</sup> However, in ischemically compromised myocardium the utilization of free fatty acids decreases whereas the use of exogenous glucose is preserved or accelerated.<sup>9,10</sup> This finding is the rationale for the use of <sup>18</sup>F-2-fluoro-2-deoxyglucose (<sup>18</sup>FDG) as a radiolabeled tracer of exogenous glucose metabolism in PET to measure viability. In combination with a flow tracer, such as <sup>13</sup>N-ammonia, a visual “mismatch” with augmented uptake of glucose relative to blood flow is indicative of hibernating myocardium.<sup>11,12</sup> Dysfunctional areas with preserved blood flow and preserved uptake of glucose may reflect stunned myocardium. As exogenous glucose

utilization of myocytes can be increased by a high-carbohydrate meal or insulin infusion, current viability protocols include standardization of metabolic conditions during examination.<sup>13,14</sup>

Recent studies have also demonstrated the accuracy and feasibility of <sup>18</sup>F-FDG and SPECT in the detection of viable myocardium.<sup>15</sup> Despite the fact that SPECT is widely available and less expensive than PET, the method is rarely used for detecting viable myocardium. The need for an ultra-high-energy collimator has limited its routine use. Other groups have used <sup>11</sup>C-acetate, a tracer of tricarboxylic acid cycle flux, with PET. This tracer allows assessment of myocardial oxygen consumption, which is known to be preserved in hibernating myocardium.<sup>16,17</sup> However, the short half-life of the tracer (about 20 min) limits its use to PET centers that have a cyclotron on site.

### Cell membrane integrity assessed by SPECT

Since the 1970s <sup>201</sup>Tl has been widely used as a single-photon tracer for myocardial perfusion imaging. <sup>201</sup>Tl is a monovalent, heavy metal, cation crystal with a crystal radius similar to that of K<sup>+</sup>. The cellular uptake of <sup>201</sup>Tl, like that of K<sup>+</sup>, involves the active transport of the ion by Na-K-ATPase and therefore maintains cell membrane integrity.<sup>18</sup> The high first-pass extraction by the myocardial tissue of approximately 85% and the linear relationship of tracer uptake and myocardial blood flow over a wide range make this tracer a suitable agent to assess coronary blood flow, providing images are acquired soon after tracer injection.<sup>19</sup> After initial uptake of <sup>201</sup>Tl, there is a continuous exchange of <sup>201</sup>Tl between perfused, viable myocardium and the blood pool. This process of continuous exchange forms the basis of <sup>201</sup>Tl redistribution, identifying in a second set of images regions with hypoperfused viable myocytes 3 to 4 h after tracer injection by delayed defect resolution.<sup>20</sup> Several animal studies have shown that the redistribution noted in delayed images represents an absolute reduction in thallium concentra-

tion in regions with normal perfusion, along with an absolute increase in the concentration in hypoperfused regions.<sup>21,22</sup> A variety of protocols have been proposed to further improve the sensitivity of the method. Some authors have suggested late acquisition 18 to 24 h after tracer injection, because some regions with viable myocardium have shown a further resolution of <sup>201</sup>Tl defect compared with images acquired 3 to 4 h after injection.<sup>23</sup> Others have suggested the administration of a first dose of <sup>201</sup>Tl under stress conditions to detect stress-induced ischemia, and the administration of a second dose after 3 to 4 h imaging at rest (stress-redistribution-reinjection imaging).<sup>24</sup> Obviously, the reinjection of thallium immediately after redistribution imaging facilitates the <sup>201</sup>Tl uptake in hypoperfused but viable myocytes by augmentation of the blood concentration of the tracer.

### Mitochondrial function assessed by SPECT

Further research resulted in the development of <sup>99m</sup>Tc-labeled cations including the isonitrile sestamibi and the phosphine compounds tetrofosmin and furofosmin. The 140 keV photon energy peak of <sup>99m</sup>Tc is optimal for imaging with a gamma-camera and produces higher quality images than those produced by <sup>201</sup>Tl. Moreover the short half-life of <sup>99m</sup>Tc permits administration of higher doses than those used by <sup>201</sup>Tl, yielding better imaging quality in a shorter acquisition time. By far the best validated tracer in this group is <sup>99m</sup>Tc sestamibi. As in the case of <sup>201</sup>Tl, the tracer uptake in myocytes is linear to myocardial blood flow over a wide range.<sup>25</sup> The complex is sequestered within mitochondria by the large negative transmembrane potential, after it has been passively transported across plasma and mitochondrial membranes, and shows no significant redistribution.<sup>26,27</sup> Therefore, <sup>99m</sup>Tc sestamibi accumulation in myocytes reflects mitochondrial function, which parallels cellular viability. Recent studies suggested that the specificity of this method can be improved by

the administration of nitrates prior to examination.<sup>28,29</sup>

### Systolic wall thickening assessed by dobutamine echocardiography

The idea of using dobutamine stress echocardiography for the detection of viable myocardium is based on the hypothesis that hibernating as well as stunned myocardium retains the ability to respond to  $\beta$ -adrenergic stimulation, resulting in augmented contractility. The technique involves stepwise administration of dobutamine. A variety of protocols have evolved. Typically the administered dose increases in 3- to 5-min stages and ranges from 2.5 to 10  $\mu\text{g kg}^{-1} \text{min}^{-1}$  dobutamine for the established low-dose protocols.<sup>30</sup> High-dose protocols with administration of up to 40  $\mu\text{g kg}^{-1} \text{min}^{-1}$  dobutamine are currently under clinical investigation. In this approach a biphasic response was noted with an initial augmentation of contractility during low-dose administration of dobutamine and a loss of contractility during administration of higher doses. This was found to be of high prognostic value in the prediction of functional recovery after revascularization in a given segment.<sup>31</sup> However, the use of this method is dependent on the investigator's experience as well as on the echogenic build of the patient.

### Systolic wall thickening assessed by dobutamine MRI

MRI has proved to be highly accurate for the assessment of cardiac anatomy and ventricular function. Its high spatial and temporal resolution combined with its independence from the investigator's experience and the anatomical build of the patient allows the assessment of systolic wall thickening and end-diastolic wall thickness with higher accuracy and better reproducibility than echocardiography.<sup>32</sup> However, the method has not yet entered general clinical use and only a few studies exist assessing the impact of dobutamine MRI on the

measurement of myocardial viability.<sup>33,34</sup>

Another promising new MRI technique, not yet validated for clinical use, is the differentiation of viable myocardium and irreversible cell damage by patterns of contrast enhancement. Rogers et al<sup>35</sup> studied 17 patients after reperfusion therapy following their first acute myocardial infarction. A first-pass acquisition, combined with a delayed acquisition about 7 min after administration of nonionic gadolinium (Gd-HP-DO3A), was made. They found that a normal first-pass signal followed by a hyperenhanced signal on delayed images indicates viability, whereas the absence of both signals suggests irreversible cell damage. Kim et al<sup>36</sup> used gadolinium DTPA, an ionic contrast agent, to measure viability following acute and chronic infarction in animal models. They concluded that hyperenhancement 20 to 30 min after administration of the contrast agent indicates irreversible cell damage. However, in both studies viability was assessed after restoration of coronary artery blood flow. Further studies must clarify whether viable myocardium can also be identified prior to revascularization by this method.

### Discordant information

Myocardial viability detection is a field of ongoing research. When considering the accuracy of the methods currently available for the detection of viability in clinical routine, it should be recognized that the number of patients currently examined by the varying methods is relatively small and heterogeneous. Moreover the techniques adopted for examination and revascularization, as well as the selection of thresholds for differentiating viable from nonviable tissue, vary with each method. Finally, differences in the accuracy of the methods may also be explained by the varying study endpoints used to assess myocardial viability, including regional and global functional recovery after revascularization and detection of viable myocardium, compared with a varying "gold standard".

However, several studies comparing two or

more currently employed modalities have shown that, depending on the different intracellular processes measured, findings concerning viability are under certain circumstances somewhat discordant.<sup>15</sup> For example, the presence of a severe perfusion defect on either 4-h <sup>201</sup>Tl redistribution or <sup>201</sup>Tl reinjection images did not preclude the possibility of residual tissue viability, as was shown by a direct comparison with PET using <sup>18</sup>F-DG metabolic imaging. Residual "metabolic" viability was demonstrated in 50% of severe defects on redistribution images and 25% of severe defects on reinjection images.<sup>37</sup> The same laboratory compared the results of stress-redistribution-reinjection <sup>201</sup>Tl SPECT imaging with <sup>99m</sup>Tc sestamibi imaging in a group of 54 patients. The investigators reported that in 36% of segments demonstrating irreversible defects on <sup>99m</sup>Tc sestamibi imaging, <sup>201</sup>Tl images indicated viable myocytes.<sup>38</sup>

Several discrepancies can be found, especially if findings regarding contractility under  $\beta$ -adrenergic stimulation are compared with nuclear tracer uptake. In a recent publication, dobutamine echocardiography, PET and <sup>201</sup>Tl

SPECT were compared with the histopathological finding of fibrosis in explanted hearts. The study revealed that contractile response, as assessed by dobutamine echocardiography, requires at least 50% viable myocytes in a given segment, whereas scintigraphic methods identify segments with about 25% viable myocytes.<sup>39</sup> This suggests that nuclear techniques may be highly sensitive for the detection of viable myocardium. A negative finding almost excludes a significant number of myocytes in a given segment being viable. This finding is in keeping with a recent study from Pagano et al.<sup>40</sup> who compared the predictive value of dobutamine echocardiography and a combined <sup>13</sup>N-ammonia/<sup>18</sup>F-DG PET protocol in identifying patients with reversibility of left ventricular dysfunction prior to coronary artery bypass surgery. Thirty patients with coronary artery disease and severely decreased left ventricular function were studied. The authors concluded that dobutamine echocardiography and PET have similar positive predictive values (68% vs 66%) in the identification of hibernating myocardium, but dobutamine echocardiography has a signifi-

Table 1. Studies with a head-to-head comparison, showing discordant viability information in patients with severely depressed left ventricular function. Sensitivity and specificity given for the study by Baumgartner et al.<sup>39</sup> are related to detection of segments containing more than 25% viable myocytes. In all other studies sensitivity and specificity are given for the prognosis of regional functional recovery after revascularization.

Study	No of patients	Method	Sensitivity %	Specificity %
<i><sup>18</sup>F-DG PET vs dobutamine echocardiography</i>				
Gerber et al <sup>41</sup>	39	PET	75	67
		Echo	71	89
Pagano et al <sup>40</sup>	30	PET	99	33
		Echo	60	62
Baumgartner et al <sup>39</sup>	5	PET	75	67
	12	Echo	66	81
<i><sup>18</sup>F-DG PET vs <sup>99m</sup>Tc sestamibi</i>				
Maes et al <sup>42</sup>	23	PET	83	91
		MIBI	92	60
<i>Dobutamine echocardiography vs <sup>201</sup>Tl reinjection</i>				
Vanoverschelde et al <sup>43</sup>	73	Echo	79	80
		<sup>201</sup> Tl	80	47
<i>Dobutamine echocardiography vs <sup>201</sup>Tl redistribution</i>				
Baumgartner et al <sup>39</sup>	12	Echo	66	81
	7	<sup>201</sup> Tl	86	63

cantly lower negative predictive value than PET (54 vs 96%;  $P < 0.0001$ ). Selected studies with a head-to-head comparison, demonstrating discordant viability information are shown in *Table 1*.

In clinical decision-making, one has to be aware of such discordant information. If the decision whether a patient with severe myocardial dysfunction should undergo revascularization therapy or heart transplantation is based on the amount of viable myocardium detected, the method chosen to measure viability may be of critical importance. One might argue that dobutamine echocardiography is the method of first choice for specific prediction of regional functional recovery in patients with depressed myocardial function in whom revascularization is contemplated, because pooled data suggest that this method has the highest specificity.<sup>15</sup> One might further argue that regions of the heart which are viable according to metabolic PET or <sup>201</sup>Tl studies, but not viable according to dobutamine echocardiography, are unlikely to improve soon after successful revascularization, because of the small amount of viable myocytes detected by nuclear techniques.<sup>44</sup> However, if regions with such discordant viability information are identified as being viable, patients may benefit from revascularization of these regions in terms of delayed improvement of regional contractility,<sup>40,44</sup> modification of the remodeling process, and prevention of adverse cardiac events.<sup>39,45–47</sup>

## Conclusion

**Current methods for the assessment of myocardial viability identify viable myocardium with varying accuracy mostly as a result of the different intracellular processes measured. Methods assessing contractility under  $\beta$ -adrenergic stimulation are less sensitive than metabolic PET imaging or <sup>201</sup>Tl scintigraphy in detecting small amounts of viable myocytes. Even if discordant viability information generally refers to regions with only a limited number of viable myocytes, patients may benefit from**

**revascularization of such regions with regard to long-term outcome.**

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