Introduction

Summary of clinical problem

Coronary heart disease is the primary single cause of left ventricular systolic dysfunction leading to heart failure in Europe. Left ventricular function is an important determinant of prognosis and parameters that reflect function, such as ejection fraction (LVEF), end-diastolic volume, end-diastolic pressure, and exercise capacity, can all be used to help predict outcome. Drugs such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II inhibitors, β-blockers, and aldosterone antagonists have improved the prognosis of heart failure, but the outcome with medical treatment remains poor. Robust randomised controlled trials of coronary revascularisation of patients with heart failure and left ventricular systolic dysfunction are lacking but are now underway. The CASS registry predated modern medical therapy and was unrandomised, but it showed that the mortality of patients with left ventricular dysfunction...
increased rapidly with reduction in LVEF, and that one-year mortality was reduced from 24% on medical therapy to 15% after revascularisation in patients with LVEF below 25%. However, perioperative mortality in patients with left ventricular dysfunction is relatively high and it is important to revascularise only patients who will obtain overall benefit. When angina is a dominant symptom, the decision is relatively simple because there are a number of well-validated methods for assessing the presence, extent, and severity of inducible myocardial ischaemia. However, when symptoms of left ventricular dysfunction dominate, the decision is more difficult because it is harder to distinguish between permanent left ventricular dysfunction and dysfunction that might improve after treatment.

Common causes of ischaemic left ventricular dysfunction are full-thickness myocardial infarction, partial-thickness infarction, myocardial stunning, and myocardial hibernation. These states are difficult to differentiate and the situation is complicated by the potential coexistence of different states in the same patient or even in the same myocardial region. Fortunately, in the last two decades experience has increased with the use of imaging techniques that can detect and assess myocardial viability, metabolism, perfusion, and function. Separately or together, these techniques can now distinguish irreversible myocardial infarction from reversible dysfunction with varying degrees of accuracy. The techniques include nuclear imaging, echocardiography, magnetic resonance imaging, X-ray transmission tomography, and electromechanical mapping of the endocardium. Each has its strengths and weaknesses, but most hospitals either do not have access to them all or lack expertise in some of them.

Aim of report

The aim of this report is to review current knowledge on myocardial hibernation and relevant imaging techniques, and to provide an algorithm for investigation when a patient presents with ischaemic left ventricular dysfunction and myocardial revascularisation is considered. It is recognised that other issues are important in such patients, including mitral valve function, ventricular synchrony, and pulmonary hypertension, but these are beyond the scope of this report.

Definitions

Terms commonly used to describe different myocardial states are “viable”, “stunned”, “hibernating”, “infarcted”, and “scarred”, but the literature is complicated by inconsistent use of the terms. Common problems are to equate infarcted myocardium with irrecoverable dysfunction, making no allowance for partial-thickness infarction, and to equate viable myocardium with hibernation. It is particularly important to distinguish between viable and hibernating myocardium since the presence of viable myocardium does not per se imply recovery of function after revascularisation.

Viable myocardium

The term “viable” describes myocardial cells that are alive and hence also the myocardium that they constitute. This begs the question of how to define “alive” since nuclear function, metabolic function, contractile function, membrane function, etc., may not be equally affected by an ischaemic insult. Fortunately, this nicety does not normally have clinical implications. Although individual myocytes may only be viable or nonviable to a first approximation, the macroscopic myocardium in ischaemic heart disease exhibits a continuum of states from fully viable, through partially viable in areas of partial-thickness infarction, to nonviable, or scarred, in areas of full-thickness infarction with no remaining myocytes. Whether applied to a myocyte or to a segment of myocardium, the term “viable” implies nothing with regard to contractile state. Thus, viable myocardium may contract normally or it may be dysfunctional, depending on other circumstances.

Stunned myocardium

Stunning is a form of contractile dysfunction of viable myocardium caused by a brief period of ischaemia followed by restoration of perfusion. It may be the result of reperfusion injury whereby restoration of normal blood flow leads to generation of free radicals and a transitory overload of calcium within the myocytes and temporary damage to the contractile mechanism. Regional myocardial stunning has been demonstrated
after myocardial infarction that is aborted by thrombolysis, after an episode of unstable angina, and after ischaemia induced by exercise testing.11 The dysfunction may persist from an hour to several days, but function ultimately returns to normal if normal perfusion is maintained.

Hibernating myocardium

Hibernation is also a state of contractile dysfunction in viable myocardium, but now in the setting of chronic ischaemic heart disease.12 In contrast to stunned myocardium, in which function recovers spontaneously, hibernating myocardium requires an intervention such as revascularisation for recovery. Hibernating myocardium is therefore normally defined as viable but dysfunctional myocardium that improves in function after revascularisation, but it is possible that medical therapy might also be effective in relieving hibernation by abolishing ischaemia.13 The definition, of course, assumes that revascularisation is successful and that the procedure itself does not lead to damage of the relevant area of myocardium.

It is important to distinguish between retrospective and prospective definitions of hibernation. Myocardium cannot strictly be defined as hibernating until improvement of contraction after intervention has been demonstrated. However, identification of hibernation is needed preoperatively for patient management and so a number of prospective definitions are used in the imaging literature. For instance, in positron emission tomography (PET), reduced ammonia uptake with normal or increased 2-fluorodeoxyglucose (FDG) uptake (PET mismatch) has been used to define hibernation, but this is a surrogate definition. A similar surrogate definition that is commonly used is "viable and dysfunctional myocardium", but this is less reliable because hibernation may be only one cause of viable myocardium that fails to contract. Others may be tethering caused by subendocardial infarction or neighbouring transmural infarction, and remodelling with loss of mechanical advantage. The demonstration of inducible ischaemia in the relevant section of myocardium is therefore a helpful addition to the definition since hibernation is an ischaemic syndrome and it is unlikely to be present in the absence of inducible ischaemia.14 Thus, the most useful surrogate definition of hibernation is viable and dysfunctional myocardium in which impaired perfusion reserve leads to inducible ischaemia.

Because we do not fully understand the pathophysiological mechanisms underlying stunning and hibernation, it is better to avoid including these mechanisms in their definition. For instance, hibernation was originally defined as "a state of persistently impaired myocardial and left ventricular function at rest due to reduced coronary blood flow that can be partially or completely restored to normal if the myocardial oxygen supply/demand ratio is favourably altered."12 It is still controversial whether or not perfusion is reduced at rest,15 although we know that it is not always reduced.16 This aspect of the definition is therefore better omitted.

Morphology of hibernation

Morphological findings in chronic hibernation

Light microscopy

Animal models of chronic myocardial hibernation are rare so it has been difficult to determine the underlying pathological mechanisms. In particular, the state of resting myocardial perfusion and extent of structural changes are debated.15 17 It was initially assumed that the recovery of function when hibernating myocardium is revascularised must mean that structural changes are absent or minimal, as had been found in experimental models of stunned myocardium. However, biopsies taken from areas of viable but dysfunctional myocardium at the time of coronary bypass grafting in human patients have shown quite severe changes of the sarcomeres, intracellular space and organelles, the cardiomyocytes themselves, and extracellular matrix.

There is a mixture of normal, atrophied, and hypertrophied myocytes, with or without evidence of necrosis. Cells with partial or complete loss of intracellular contractile proteins are seen, sarcomeres and myofibrils are lost, and there is intracellular accumulation of glycogen18 19 and variable intercellular fibrosis.20 There is also new expression of proteins such as smooth muscle α-actin, titin, and cardiotin, which are normally found in foetal tissue as opposed to adult myocardium, so the changes have been described as dedifferentiation.21 There is therefore a variety of cellular and subcellular degeneration with varying degrees of degeneration and fibrosis, and the likelihood of recovery of function after revascularisation is related to the extent of myocyte injury and amount of replacement fibrosis.22 It is not clear, however, whether these changes are the cause or effect of hibernation. It has been suggested that hibernation, which is a downregulation of myocardial function, is followed by “downregulation” of structure and, if adaptive processes are insufficient, focal cell death and apoptosis. The early changes may be reversible before significant structural disorders occur, but the loss of myocytes is obviously not reversible so long-term hibernation may lead to irreversible loss of myocardial function.

Electron microscopy and immunohistochemistry

Electron microscopy shows degenerative changes of cell organelles, such as loss of sarcomeres, initially in perinuclear areas, deterioration of sarcoplasmic reticulum, fragmentation of rough sarcoplasmic reticulum, loss of T-tubules,18 23 24 and enlargement of the extracellular space, which is filled with cellular debris, extracellular matrix, macrophages, and fibroblasts.25 A frequent finding is dispersion of nuclear chromatin. Calcium precipitates in altered sarcomeres but not in unaltered mitochondria.26 There is disorganisation and reduced expression of contractile proteins, such as myosin and actin, and of cytoskeletal proteins, such as desmin, titin, α-actinin, and vinculin, both the proteins themselves and their messenger RNA.27 There is a reduction of A-type lamins suggesting dedifferentiation.28
Death of cells by apoptosis involves a number of characteristic changes, but steps in this cascade have been found in only a few cells in chronic hibernation and there is conflicting evidence on whether apoptosis is a significant feature of hibernation. Although the percentage of apoptotic cells reported in hibernation varies with the method of detecting apoptosis, it is likely that the true percentage is less than 10%.

Animal models of chronic hibernation

In animal models of short-term hibernation, a moderate reduction of resting myocardial perfusion leads to reduced contraction at rest but contractile reserve in response to inotropic stimulation. There is an initial reduction of creatine phosphate levels with lactate production, but creatine phosphate recovers and there is a return to normal lactate consumption in the later equilibrium state. However, when there is more severe reduction of perfusion then inotropic stimulation leads to necrosis. Other features of these models are patchy endocardial necrosis, myofibrillar disruption, downregulation of phospholamban and calcium-ATPase in the sarcoplasmic reticulum, and apoptosis. The syndrome of an anomalous left coronary artery arising from the pulmonary artery is a possible natural model of hibernation because of low perfusion pressure and chronic hypoxia of the left coronary bed. When this syndrome is mimicked in pigs, however, adaptation is either insufficient or too slow to maintain cellular structures and necrosis occurs.

Therefore, a stable chronic model of hibernation that does not result in cell death has not been established, but since there is also evidence of cell death in human hibernation this is not surprising. It is likely that hibernation is not a stable situation and that there is deterioration and loss of potential for recovery of function with time.

Spectrum of changes in hibernation

Although the evidence is circumstantial, it is proposed that there is a spectrum of change in chronic hibernation and that in the face of recurrent ischaemia or imbalance of oxygen supply and demand, the changes evolve through the spectrum and become irreversible. So far, only abolition of ischaemia by revascularisation can arrest this process and hopefully reverse the changes if performed soon enough. It is not known whether treatment to stabilise cell membranes or to prevent apoptosis might be helpful but this is currently under investigation.

Clinical aspects of myocardial viability and hibernation

Prevalence of myocardial hibernation

A systematic large-scale study of the prevalence of myocardial hibernation is not available and the issue is further confused by different definitions of the syndrome. However, in patients with chronic left ventricular dysfunction the frequency of segmental recovery of function after revascularisation, as well as the proportion of patients showing functional recovery, can be established (Fig. 1). Recovery is seen, on average, in 55–60% of dysfunctional segments, even in patients with baseline ejection fraction below 40%. The true prevalence of recoverable dysfunction is probably underestimated because the completeness of revascularisation is seldom assessed, and because segments with advanced morphological changes may take up to one year to recover function.

Relevant clinical settings

In theory, the reversibility of left ventricular dysfunction is relevant in all presentations of ischaemic heart disease, including unstable angina, reperfused myocardial infarction, and heart failure. However, in acute infarction and unstable angina, the efficacy of early revascularisation usually means that the assessment of myocardial viability is either impractical or only of academic interest. The importance of myocardial stunning, hibernation, and persistent ischaemia in patients with acute coronary syndromes is, however, poorly defined. When patients present in the subacute stage of infarction, additional testing is required to identify those with viable but jeopardised myocardium in whom revascularisation may be warranted.
Q waves on the electrocardiogram (ECG) were originally revascularisation over medical treatment (Fig. 2)59 and modern medical management of heart failure favoured to abolish ischaemia.58 Studies before the advent of revascularisation would be to improve left ventricular function rather than angina because the main indication for revascularisation relevant in patients with heart failure without limiting angina or heart failure. Hibernation is, of course, not always clarified whether the dominant symptom is angina, where hibernation is most relevant, and they have not always included patients with severe dysfunc-

The main value of noninvasive assessment of viability and hibernation is in the more severely and chronically disabled patient, in whom the outcome without intervention is poor but the risk of revascularisation is high.54 In patients with LVEF below 35%, the perioperative, in-hospital and one-year outcome is better when the need for revascularisation is guided by preoperative assessment of viability and hibernation.55 Even in patients being considered for cardiac transplantation, viability assessment can alter the initial choice of treatment (medical, revascularisation, or transplantation) in 57% of cases.56

It is important to note that there are no prospective controlled studies of revascularisation in patients with hibernating myocardium, and no randomised comparisons between revascularisation and medical therapy. The strongest evidence to support revascularisation will come from randomised trials, but there is a reasonable body of nonrandomised evidence supporting revascularisation of hibernating myocardium.57 It is also important that the retrospective and observational studies that have been made in patients with ventricular dysfunction have not always included patients with severe dysfunction, where hibernation is most relevant, and they have not always clarified whether the dominant symptom is angina or heart failure. Hibernation is, of course, most relevant in patients with heart failure without limiting angina because the main indication for revascularisation would be to improve left ventricular function rather than to abolish ischaemia.58 Studies before the advent of modern medical management of heart failure favoured revascularisation over medical treatment (Fig. 2)59 and the recommendation at that time was that "surgical coronary revascularisation should be undertaken instead of heart transplantation whenever myocardial viability (hibernation) is detected".60

Application of imaging techniques

Electrocardiography

The Q wave
Q waves on the electrocardiogram (ECG) were originally thought to indicate full-thickness myocardial infarction and so the relationship between Q waves and myocardial viability is of interest. In fact, there is no relationship between the presence and extent of Q waves after myocardial infarction and infarct size assessed by myocardial perfusion imaging, and up to 60% of regions with Q waves have viable myocardium detected by imaging techniques.61-63 QR complexes are not more likely to be associated with viable myocardium than QS complexes,64 and there is no correlation between the QRS score and left ventricular ejection fraction after myocardial infarction.65 Thus, the QRS complex is not an adequate marker of myocardial viability in clinical practice.66

The ST segment
ST-segment elevation at rest in leads with Q waves is associated with more severe wall-motion abnormalities, less contractile reserve and greater end-systolic volume.67 In the extreme case, this is seen as the persistent ST elevation of aneurysm formation. In contrast, ST elevation developing during exercise is a marker of maintained viability, and late improvement in LV function after myocardial infarction is more common when the ST segment is elevated during dobutamine echocardiogra-

![Table: Risk ratios for survival following medical or surgical therapy in patients with moderate-to-severe left ventricular dysfunction](https://academic.oup.com/eurheartj/article-abstract/25/10/815/567325)
**18F-fluoro-2-deoxy-D-glucose (FDG)** is a glucose analogue. The strength of positron emission tomography (PET) as an imaging technique lies in the versatility of positron-emitting radionuclides that can be incorporated into important biochemical molecules. Not only can the distribution of these molecules be imaged, but their uptake can be quantified. In this way, it is possible to assess myocardial perfusion, glucose utilisation, fatty acid uptake and oxidation, oxygen consumption, contractile function, and presynaptic and postsynaptic neuronal activity.

**FDG and ammonia**

18F-fluoro-2-deoxy-D-glucose (FDG) is a glucose analogue that is taken up by viable cardiac myocytes in the same way as glucose, but its subsequent metabolism is blocked and it remains within the myocyte. FDG uptake is due to a relative increase in uptake because of metabolic embarrassment and preferential myocardial consumption of glucose. FDG uptake is related to viability than to dysfunction alone.

**Positron emission tomography**

The strength of positron emission tomography (PET) as imaging technique lies in the versatility of positron-emitting radionuclides that can be incorporated into important biochemical molecules. Not only can the distribution of these molecules be imaged, but their uptake can be quantified. In this way, it is possible to assess myocardial perfusion, glucose utilisation, fatty acid uptake and oxidation, oxygen consumption, contractile function, and presynaptic and postsynaptic neuronal activity.

**Hybrid and gamma camera approaches**

PET imaging is not widely available because of its expense and complexity. Even when a PET camera is available, imaging may be restricted to FDG because the half-lives of 13N and 15O are too short to allow ammonia and water imaging without an on-site cyclotron. Thus, FDG imaging for myocardial viability has been combined with single-photon perfusion tracers, such as thallium, MIBI, and tetrofosmin. This hybrid approach has proved successful. It is now also possible to image FDG using a conventional gamma camera, either using a single head with 511 keV collimation (high-energy SPECT), or using opposed heads without collimation and taking advantage of coincidence detection of 511 keV photons (gamma camera PET).

**Other metabolic tracers**

Because fatty acids are an important source of energy for the myocardium, positron-emitting fatty acid analogues such as 11C-palmitate and 18F-thiaheptadecanoic acid (FTHA) have been also used to assess myocardial viability.
ity. Although fatty acid oxidation is preserved in hibernating myocardium, the clinical results with these tracers have not been encouraging. Thallium-201 has been used extensively for identifying myocardial viability and hibernation; it was the first tracer to be used for this purpose. However, it has a number of unfavourable properties, such as a low-energy X-ray emission and a long half-life, leading to appreciable radiation exposure to patients. The tracer behaves as a potassium analogue and myocardial uptake depends upon regional flow and upon an intact sarcolemmal membrane to facilitate transport. Therefore, thallium provides information on both perfusion and cell viability. A simple stress-redistribution protocol can underestimate the amount of viable myocardium present and alternative protocols have been used. These include imaging from 8 to 72 h after stress injection, reinjection of tracer at rest on the same day as the stress injection, a resting injection on a separate day, or adjuncts aimed at speeding redistribution towards the pattern of viability, such as ribose or nitrates. Late-redistribution imaging shows increased uptake in up to 54% of defects that are fixed 4 h after stress injection. Reinjection leads to increased uptake in 49% of segments and nine studies using this technique had positive and negative predictive accuracies of 69% and 89%, respectively, for regional improvement. The most widely reported technetium agent is Tc-99m-2-methoxyisobutylisonitril (MIBI). Most studies have assessed viability rather than hibernation, some comparing the results with those of PET or histology, and others comparing the relative uptake of MIBI and thallium after quantitative analysis. Some studies have found MIBI to be inferior to thallium for identifying viability, but others have found the two to be comparable. There is less experience with technetium-labelled tetrofosmin than with MIBI in the identification of viability. Some studies have found it to be less sensitive than thallium, but it is likely to perform similarly to MIBI.
In regions with reduced tracer uptake, both thallium and MIBI uptake have been improved by sublingual or intravenous nitrates, which improve resting myocardial perfusion.\textsuperscript{110} 126 127 Sciagra and colleagues\textsuperscript{128} showed that defects were less severe with nitrates than without nitrates, and the identification of hibernation was improved. Moreover, Bisi and colleagues\textsuperscript{128} showed that improvement in tracer uptake with nitrate in itself predicted hibernation. It is likely that these effects are also applicable to tetrofosmin imaging.

**ECG-gated SPECT**

ECG gating of technetium-perfusion tomograms is now routine and these images provide measures of global and regional function that have been validated against higher-resolution tomographic imaging techniques.\textsuperscript{129} 132 Although the SPECT images are not high resolution, it is possible to assess myocardial thickening, as well as motion, since myocardial counts are linearly related to myocardial thickness. Thickening is a better assessment of regional function than motion because infarcted regions can appear to move if dragged by neighbouring normal regions, and normal regions can appear akinetic if regional motion is opposed by translation of the whole heart. Simultaneous assessment of myocardial perfusion, viability, and function has already proved clinically valuable in assessing patients with ischaemic left ventricular dysfunction,\textsuperscript{133} 134 and gated imaging during dobutamine stress will provide further information in terms of contractile reserve.\textsuperscript{135}

**Fatty acids**

Although many different fatty acids have been used for myocardial imaging in patients with ischaemic heart disease, most experience has been obtained with $\beta$-methyl-iodo-pentadecanoic acid (BMIPP) labelled with iodine-123. Normal myocardium metabolises fatty acids in preference to glucose, but for a period of time after an acute ischaemic insult, or when myocardium is jeopardised by recurrent stunning, resting perfusion, or hibernation, glucose is metabolised in preference and a defect on fatty-acid imaging appears. If the defect is more profound than expected from the amount of viable myocardium assessed by a viability tracer such as thallium, then metabolic embarrassment can be assumed. The viability-BMIPP mismatch suggestive of hibernating myocardium is therefore in the opposite direction to perfusion-metabolism mismatch of PET.

Initial clinical studies with BMIPP confirmed the expected prolongation of myocardial retention and demonstrated excellent definition of normal myocardium.\textsuperscript{136} Subsequent studies showed an inverse relation between myocardial fibrosis and BMIPP uptake in regions of chronic dysfunction undergoing revascularisation.\textsuperscript{137} The viability-BMIPP mismatch pattern has also been shown to correspond with thallium redistribution\textsuperscript{138} 139 and preserved contractile reserve after myocardial infarction.\textsuperscript{140} In a study of hibernating myocardium with assessment of function before and after revascularisation, combined thallium and BMIPP imaging had a sensitivity of 94% and specificity of 50% for predicting recovery of function.\textsuperscript{141} Thus, fatty-acid imaging may be of value in assessing patients with ischaemic left ventricular dysfunction, although further experience is required to know if there is a benefit in assessing fatty acid metabolism in addition to perfusion and viability using other tracers.

**Imaging of innervation**

The autonomic nervous system plays an important role in the regulation of cardiac function and the regional distribution of cardiac nerve terminals can be visualised using scintigraphic techniques. A number of labelled analogues of noradrenaline have been investigated, but the most commonly used are iodine-123 meta-iodobenzyl guanidine (MIBG)\textsuperscript{142} and $^{11}$C-hydroxyephedrine,\textsuperscript{143} 144 $^{11}$C-adrenaline,\textsuperscript{146} and $^{18}$F-fluorodopamine\textsuperscript{147} have also been used. When imaging with MIBG, the ratio of heart-to-mediastinal counts is used as an index of tracer uptake, and regional distribution is also assessed from tomographic images. The rate of clearance of the tracer from the heart is sometimes measured, but there are no widely accepted normal values for these measurements.

In patients with heart failure secondary to ischaemic heart disease or cardiomyopathy, reduced MIBG uptake is an adverse prognostic sign,\textsuperscript{148} 150 presumably indicating advanced disease with denervation. Treatment with $\beta$-blockade leads to parallel improvements in MIBG and symptoms,\textsuperscript{151} and similar observations have been made after cardiac transplantation.\textsuperscript{152} Further studies are required to ascertain the clinical value of these observations.

**Echocardiography**

**Stress echocardiography**

Stress echocardiography allows inducible myocardial ischaemia to be detected indirectly by direct visualisation of the consequential left ventricular dysfunction.\textsuperscript{153} 154 Stress can be induced using dynamic exercise or pharmacological alternatives.\textsuperscript{155} Imaging is difficult during dynamic exercise and it is sometimes additionally limited by the absence of a suitable echocardiographic window. It is therefore normally performed on cessation of exercise and within 2 min because exercise-induced abnormalities are normally transitory. In patients who are unable to exercise, dobutamine and dipyridamole are alternatives,\textsuperscript{156} but dobutamine is now more common\textsuperscript{157} because it more readily induces ischaemia as opposed to heterogeneity of perfusion. The stress-induced abnormalities are normally reported as a wall-motion score that represents a combination of their extent and magnitude.

Myocardial infarction, particularly transmural infarction, leads to thinned and akinetic segments at rest. However, if the function of an akinetic segment improves with stress, this implies the presence of viable myocardium.\textsuperscript{158} 159 Low doses of dobutamine (5 $\mu$g/kg/min) are normally sufficient to provoke this response and, if there
is also inducible ischaemia, then a biphasic response is seen with initial improvement in function and deterioration at higher doses. The extent of myocardial hibernation determined in this way predicts outcome after revascularisation. The reported accuracy of stress echocardiography for predicting recovery of segmental function after revascularisation varies, with sensitivities of 70% to 85% and specificities of 80% to 90%. This variation may, in part, reflect the operator-dependence of the technique. When conventional first-harmonic imaging does not provide adequate images, then both harmonic imaging and the use of intravenous blood-pool contrast can improve endocardial definition.

Limitations of conventional cross-sectional techniques are their subjective assessment of regional myocardial function, their assessment of mainly systolic and not diastolic function, and the fact that they do not assess long-axis function. Long-axis ventricular function reflects the mechanical behaviour of the subendocardium and this is the region that is most vulnerable to ischaemia. Amplitude, velocity, and timing of long-axis motion can be studied in detail by M-mode and tissue Doppler echocardiography. In patients with ischaemic left ventricular dysfunction, increased amplitude of long-axis motion during dobutamine is a marker of viable myocardium in the relevant segment. In contrast to cross-sectional echocardiography, these measurements are objective and reproducible and they are therefore an attractive addition when assessing myocardial viability and hibernation by echocardiography.

**Myocardial contrast echocardiography**

Microbubbles are good ultrasonic contrast agents that can be given intravenously to enhance the blood-pool signal and, hence, endocardial edge detection. The degree of myocardial enhancement is related to myocardial blood volume. Most clinical experience with contrast echocardiography has been with intracoronary injections. The technique has been used to show the area at risk during acute coronary occlusion and to assess the extent of tissue reperfusion after opening an acutely occluded artery. More recently, it has been used to assess the haemodynamic significance of coronary stenoses, although with variable success. The most promising approach for the assessment of perfusion is to apply pulses of ultrasound energy that destroy microbubbles, and to study the relationship between the frequency of destructive pulses and the wash-in of fresh contrast. The role of contrast echocardiography in assessing myocardial hibernation is promising.

**Radionuclide angiocardiology**

Radionuclide ventriculography does not visualise the myocardium, although regional endocardial motion can be deduced from changes in the blood pool throughout the cardiac cycle. It is not commonly used in the assessment of myocardial viability, although it is an accurate and reproducible technique for the assessment of ventricular function that has been used in many studies for the assessment of patients with ischaemic left ventricular function before and after revascularisation. The technique is highly reproducible and changes of left ventricular ejection fraction of more than 5% lie outside the interstudy variability. Such reproducibility cannot be achieved by echocardiography. Other techniques for serial assessment of left ventricular function include magnetic resonance imaging and ECG-gated SPECT.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) has an established role in cardiovascular imaging, providing important information on anatomy, function, and blood flow. It has some limitations, including its temporal resolution, the need for breath-holding with some acquisition sequences, and difficulties with claustrophobic patients and pacemaker-bearers. It provides two different approaches to the assessment of patients with chronic ischaemic left ventricular dysfunction. One is to assess myocardial morphology, function at rest, and contractile reserve during pharmacological stress. This approach is well validated. The other approach is to image myocardial infarction and to evaluate the microcirculation using paramagnetic contrast agents.

**Myocardial thickness and contractile reserve**

Because of its high-resolution and high-contrast images, MRI is now the standard against which other techniques are compared for the measurement of ventricular volumes, ejection fraction, myocardial mass, and regional wall motion. Spatial resolution is 1–2 mm and temporal resolution is between 20 and 50 ms. Even shorter acquisition times can be achieved, up to real-time imaging, although at the expense of spatial resolution and the signal-to-noise ratio.

Depending on the transmural extension, infarcts more than four months-old may become akinetic and thinned. Old infarctions with an end-diastolic myocardial thickness of less than 5.5 mm have significantly reduced FDG uptake and this has been used as the threshold for clinically significant myocardial viability. This threshold has 94% sensitivity but 52% specificity for predicting recovery of regional function 3 months after revascularisation. Thus, segments of less than 5.5 mm in thickness are not very likely to be hibernating, but segments of more than 5.5 mm in thickness may be hibernating or may simply consist of partial-thickness infarction.

Contractile reserve can also be evaluated by dobutamine MRI with a sensitivity of 89% and specificity of 94% for detecting hibernation. A strength of MRI is the ability to measure parameters of global and regional function accurately and reproducibly, although this is time-consuming and simple visual analysis is equally specific but slightly less sensitive for detecting hibernation. In a direct comparison between dobutamine MRI and thallium and tetrofosmin SPECT in patients with ischaemic left ventricular dysfunction undergoing revascularisation, MRI had a low sensitivity (50%) but high specificity (81%), whereas the nuclear techniques were
more sensitive, but less specific for predicting recovery of regional function.\textsuperscript{115}

Contrast-enhanced myocardial imaging
A developing technique is the use of extracellular para-
magnetic contrast agents, such as gadolinium-DTPA. These exchange rapidly between the intravascular and extracellular interstitial space, but they do not pass through the intact membranes of cardiac myocytes so they are not direct markers of viability. They have, however, been used to detect regional abnormalities of myocardial perfusion using first-pass techniques\textsuperscript{200,201} and to provide information on myocardial viability by imaging the tissue phase early (within 10 min) and later (10–60 min), after the first pass.\textsuperscript{202} First-pass imaging of perfusion has not yet developed into a clinically robust technique, but tissue-phase imaging has already found clinical application.

The mechanism of late enhancement is not clear, but it is possibly related to an increase of the extracellular matrix late after infarction.\textsuperscript{203,204} In some of the original studies, areas of acute infarction were enhanced late after contrast injection, presumably because of entrapment of the contrast agent in the interstitial oedema associated with cell necrosis and capillary plugging.\textsuperscript{205} Ninety percent of areas that were enhanced were nonviable,\textsuperscript{206} and infarcted areas that did not enhance corresponded with microvascular ob-
struction,\textsuperscript{207} which is associated with an adverse out-
come.\textsuperscript{208} Using more recent acquisition techniques, late contrast enhancement is seen in regions of old infarction\textsuperscript{209} that are nonviable by thallium scintigraphy,\textsuperscript{210} and the higher resolution of MRI makes it more sensitive than other techniques for nontransmural in-
farction.\textsuperscript{211,212} Animal studies have shown excellent agreement between infarct size and extent of late contrast enhancement\textsuperscript{213} and the technique has good reproducibility.\textsuperscript{214} Using these techniques it has been demonstrated that functional recovery after revascu-
larisation of dysfunctional myocardium is less likely to occur with increasing transmural extent of hyperen-
hancement.\textsuperscript{215}

X-ray transmission tomography
Mechanical X-ray transmission tomography has high spa-
tial resolution but poor temporal resolution, and images of a moving structure, such as the heart, have to be triggered to a relatively stationary phase of the cardiac cycle, such as end-diastole. Electron beam X-ray trans-
mission tomography (EBT) has a much higher temporal resolution, although it does not currently image as many slices as a modern multidetector mechanical machine. Whichever type of scanner is used, the technique is super-
factorially similar to magnetic resonance imaging in its applica-
tions, although its limitations include much less native contrast between different tissues, restrictions in the orientation of oblique planes, and the need to use ionising radiation and iodinated contrast media.

X-ray transmission tomography with contrast provides accurate and reproducible measures of ventricular mass\textsuperscript{216} and global and regional function.\textsuperscript{217} and this in-
formation can be acquired at rest and during dobutamine stress.\textsuperscript{218} Thus, the technique could provide similar information on myocardial viability and hibernation as echocardiography or magnetic resonance imaging, but no studies have been published in this setting.

Imaging of the first pass of an iodinated contrast medium through the central circulation and myocardium allows myocardial perfusion to be measured in absolute terms\textsuperscript{219} and the technique has been validated in an ex-
pertimental setting.\textsuperscript{220} Contrast has been used to image myocardial infarction in both experimental\textsuperscript{221,222} and clinical settings.\textsuperscript{223,224} The findings have been similar to the observations made with magnetic resonance contrast studies, namely, reduced early contrast in areas of in-
farction and enhanced delayed contrast on late imaging. The technique has been used to assess myocardial via-
bility,\textsuperscript{225} but not hibernation.

Invasive X-ray ventriculography and coronary angiography
X-ray contrast ventriculography played an early role in demonstrating that regional systolic dysfunction in pa-
ients with chronic ischaemic heart disease could be re-
versible following successful revascularisation.\textsuperscript{226} In the 1970s, it was shown that transitory improvement in regional contraction in response to stimuli such as intra-
venous adrenaline or postextrasystolic potentiation predicted recovery of function after revascularisa-
tion,\textsuperscript{227,228} but noninvasive imaging techniques are now accepted as more versatile for assessing contractile reserve.

In clinical practice, however, preoperative coronary angiography and contrast ventriculography are essential for patient management. Left ventricular ejection frac-
tion and volumes are important indicators of progno-
sis\textsuperscript{229,230} and these can be measured from the contrast ventriculogram, just as they can from other imaging techniques. Coronary arteriography is also essential for defining the causal relationship between ventricular dysfunction and coronary anatomy. Whenever dysfunc-
tion is observed in the absence of obstructive coronary disease, other causes of dysfunction, such as alcohol abuse, tachycardia-induced cardiomyopathy,\textsuperscript{231} or val-
cular disease, should be excluded. The choice between surgical or percutaneous revascularisation likewise de-
deps on the findings at coronary arteriography, which include the technical feasibility of percutaneous inter-
vention, the suitability of distal vessels for graft anas-
tomosis, and the availability of potential graft conduits.

Electromechanical mapping
Electromechanical endocardial mapping using a nonflu-
oroscopy catheter-based system (NOGATM, Biosense) was first described in 1996.\textsuperscript{232} The system combines nonfluorescopic catheter navigation and real-time, three-dimensional reconstruction of the endocardial surface providing simultaneous electric, anatomic, and
mechanical mapping of the endocardium. Anatomic localisation of the catheter tip is provided by triangulation from three magnetic coils positioned around the chest. The system is reproducible and accurate, and comparisons with echocardiography have shown that both local shortening and unipolar voltage agree well with echocardiographic wall-motion abnormalities.

Because myocardial ischaemia and infarction have significantly different endocardial electrograms, the amplitude of the unipolar electrogram has been proposed as an indicator of myocardial viability. Infarct size measured by electromechanical mapping compares well with pathology and echocardiography, and the boundary between normal and infarcted myocardium can be identified precisely by both electrical and mechanical patterns. Similar comparisons have been made with SPECT images, and electrogram amplitude and linear shortening are normal in areas with inducible perfusion abnormalities, but reduced in areas with fixed perfusion defects. In a pig model of hibernation, local shortening was reduced but electric activity was preserved. Early clinical studies of patients with left ventricular dysfunction undergoing revascularisation suggest that electromechanical mapping is able to predict recovery of regional function, but large clinical studies are required to confirm these findings.

Comparison of imaging techniques

As discussed above, several noninvasive techniques can identify viable and hibernating myocardium, each of them focusing on a different aspect. The four most commonly used approaches are FDG PET, thallium SPECT using a reinjection or a rest-redistribution protocol, technetium SPECT using gated or nongated images, and dobutamine echocardiography. These techniques have been used in patients with chronic ischaemic left ventricular dysfunction to predict improvement of regional and global function, improvement of heart failure symptoms, and long-term event-free survival. This section summarises the performance of the commonly used studies in clinical practice.

Regional left ventricular function

In a recent meta-analysis, all available studies of regional left ventricular function in patients with ischaemic left ventricular dysfunction before and after revascularisation were pooled. The majority used echocardiography, although MRI was used in some and this is preferable because of the higher resolution of the technique and better quantification. Some studies may be biased by lack of blinding with regards to preoperative function and by using the technique under investigation (for instance, echocardiography) as the standard for pre- and postoperative function. Weighted positive and negative predictive accuracies were calculated from the pooled data with their 95% confidence intervals. The results are summarised in Fig. 3. For each technique, the negative predictive value was higher than the positive predictive value. Dobutamine echocardiography had the highest positive predictive value (P < 0.05 vs. others), with intermediate values for FDG PET, rest-redistribution thallium SPECT, and technetium SPECT, and the lowest value for reinjection thallium SPECT (P < 0.05 vs. others). FDG PET, reinjection thallium SPECT, and dobutamine echocardiography had the highest negative predictive values, with lower values for rest-redistribution thallium SPECT and technetium SPECT.

However, most of the studies averaged in Fig. 3 do not compare imaging techniques in the same patients. In order to examine more closely the differences between nuclear imaging and dobutamine stress echocardiography, a subset of 18 studies (563 patients) that compared the two techniques in the same patients was selected. Three of these studies used FDG PET, five used reinjection thallium SPECT, and ten used rest-redistribution thallium SPECT. Dobutamine echocardiography used a low-dose protocol in sixteen and a high-dose protocol in two studies. Nuclear imaging was more sensitive in the prediction of recovery of function than dobutamine echocardiography, whereas dobutamine echocardiography was more specific. The pooled results showed a higher negative predictive value for nuclear imaging (83% vs. 79%) and a higher positive predictive value for dobutamine echocardiography (79% vs. 63%). Even this comparison may not be completely fair since some
studies compared low-dose dobutamine echocardiography (used only to detect viability) with a thallium reinjection protocol (used to detect viability and inducible ischemia). Other studies compared rest-redistribution thallium imaging (to detect viability) with low-high dose dobutamine echocardiography (both viability and ischemia). When the analysis was restricted to comparisons of techniques assessing viability alone, 11 studies with 325 patients remained. The positive predictive values were 84% for echocardiography and 75% for nuclear imaging (P < 0.05) and the negative predictive values 69% and 80% respectively (P < 0.05) (Fig. 4). Although it is mainly supposition, the requirement to demonstrate inducible ischaemia before diagnosing hibernation is likely to increase the positive predictive value of the nuclear techniques, since this would prevent viable but dysfunctional segments caused by partial-thickness infarction or remodelling from being labelled as hibernating.

**Global left ventricular function**

Information on predicting improvement of global function is scarce, although this is probably more important from the point of view of prognosis than of prediction of improvement in regional function. The meta-analysis described above also pooled information on LVEF before and after surgery (Table 1). There was an increase in LVEF in patients predicted as having hibernating myocardium by each technique, but no improvement in those without hibernation. An important issue is how much hibernating myocardium must be present for an improvement in LVEF after revascularisation to become evident. The threshold amount of hibernating myocardium necessary to classify a patient as hibernating varies from a minimum of 8% to a maximum of 53% with a mean of 22%. Only one study used ROC analysis to assess the minimum amount of hibernating myocardium necessary to detect an improvement of global function, which was 25%. It is also important to consider how great the improvement in LVEF must be to be clinically meaningful. Most studies have considered an improvement of ≥5% (e.g., from 30% to 35%) as significant, but this is mainly because of the interstudy reproducibility of measurements of ejection fraction rather than because this value is known to be clinically significant.

**Symptoms**

Symptoms and prognosis are the most important outcomes to consider when assessing patients with left ventricular dysfunction for revascularisation. Improvement in global LV function is expected to improve symptoms and quality of life, but only a few uncontrolled and observational studies have assessed this directly in relation to revascularising hibernating myocardium. Nonetheless, there does appear to be a relationship between the extent of hibernation before revascularisation and the improvement in symptoms afterwards, and exercise capacity also improves. However, very few studies have included patients with dominant symptoms of heart failure and many patients also have angina that would be expected to improve with revascularisation.

![Fig. 4](https://academic.oup.com/eurheartj/article-abstract/25/10/815/567325/Downloaded-by-guest-on-11-January-2019)

**Table 1** Weighted mean LVEF (%) before and after revascularisation according to the presence or absence of myocardial hibernation

<table>
<thead>
<tr>
<th>Technique</th>
<th>Hibernation</th>
<th>No hibernation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVEF before</td>
<td>LVEF after</td>
</tr>
<tr>
<td>FDG PET</td>
<td>12</td>
<td>37</td>
</tr>
<tr>
<td>Thallium</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>MIBI</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>Dob echo</td>
<td>7</td>
<td>35</td>
</tr>
</tbody>
</table>

See text for abbreviations.
Prognosis

Several studies have assessed medium-term coronary event rates in patients who were managed medically or by revascularisation. Seven studies used FDG PET, four used thallium SPECT, and seven used echocardiography. There was relatively high mortality in all groups except patients with hibernating myocardium who underwent revascularisation (Fig. 5). The main shortcoming of these studies, however, is that they were retrospective and observational. Clearly, prospective, randomised studies are needed to obtain definitive conclusions on the prognostic value of revascularisation in patients with hibernating myocardium and two such studies are underway.

Summary of indications

Definition of classes

It is common practice in guidelines to classify treatments or investigations according to clinical value. Some classifications also include the strength of the evidence underlying the classes. This study group discussed whether to use a recognised system of classification or whether to adapt a system to suit its needs. It was thought better to adapt a system since no previous system has been used to describe a range of investigations that are complementary or can be used in a hierarchical fashion. It was also decided not to include an indication of the strength of the evidence underlying the classification, since randomised controlled trials have not been reported in this setting. Thus, the classifications are the consensus opinions of the writing and advisory boards based upon validation studies, comparative trials, and wide clinical experience. Table 2 explains the classification used.

Myocardial properties

Table 3 shows the classes of the imaging techniques and variants in defining important myocardial properties. There is considerable overlap in the capabilities of the techniques and for any individual property, several techniques may be class 1. However, many centres do not have access to all of the techniques and when there are competing class 1 indications, a choice between them can be made between them according to local availability and expertise.

Clinical indications

Table 3 is intended for the cardiac imager when selecting techniques to define regional myocardial properties. The referring physician or cardiologist, however, has slightly different concerns and Table 4 shows the classification of imaging techniques according to clinical setting. The patient with known ischaemic heart disease and stable left ventricular dysfunction is considered. This might typically be a patient with previous myocardial infarction who is being newly considered for further management and possible revascularisation. In the asymptomatic patient, the principal concern is to detect silent ischaemia since this may have prognostic implications and require specific treatment to improve prognosis.

Clinical algorithm

The issues are complex and do not lend themselves to a simple algorithm that covers all clinical circumstances, particularly when many centres do not have expertise in all of the imaging techniques that are potentially helpful. Fig. 6 offers a simplified algorithm for the patient who is thought to have ischaemic left ventricular dysfunction with heart failure and in whom revascularisation to improve left ventricular function is considered. The principles that it embodies are:

- The assessment of myocardial hibernation is most relevant in the patient with a principal symptom of dyspnoea rather than angina.
- Myocardial perfusion scintigraphy and stress echocardiography have similar capabilities for the detection
of viable and hibernating myocardium. In many centres the choice will depend upon availability and local expertise, and on whether the clinical question requires a sensitive or a specific technique for predicting recovery of segmental function.

- Magnetic resonance imaging will normally be reserved to assess rest and/or stress left ventricular function if further clarification is required after echocardiography and/or myocardial perfusion scintigraphy. However, if magnetic resonance imaging is readily available, it is a good alternative to thallium or technetium scintigraphy for the assessment of viability.

- There is evidence from nonrandomised studies supporting revascularisation for the treatment of myocardial hibernation and an indication that medical therapy with carvedilol may be helpful. There are no published randomised comparisons between revascularisation and medical therapy in patients with myocardial hibernation, although one is ongoing. Revascularisation is, however, recommended by many authorities.

**Table 3** Classes of imaging techniques for the assessment of important myocardial properties

<table>
<thead>
<tr>
<th>Viability</th>
<th>Function</th>
<th>Perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>FDG</td>
<td>Inv</td>
<td>Inv</td>
</tr>
<tr>
<td>NH3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GC FDG</td>
<td>Inv</td>
<td>Inv</td>
</tr>
<tr>
<td>MPS</td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>FDG</td>
<td>Inv</td>
<td>Inv</td>
</tr>
<tr>
<td>Thallium</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Technetium</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gated</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Echo</td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Contrast</td>
<td>Inv</td>
<td>–</td>
</tr>
<tr>
<td>MRI</td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Stress</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Contrast</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>RNV</td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>EBT</td>
<td>Inv</td>
<td>2</td>
</tr>
<tr>
<td>XR angiogram</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>EM mapping</td>
<td>Inv</td>
<td>Inv</td>
</tr>
</tbody>
</table>

The classes are defined in Table 2. –, technique not capable of providing this information; Inv, investigational; PET, positron emission tomography; MPS, myocardial perfusion scintigraphy; FDG, 2-fluorodeoxyglucose; NH3, ammonia; GC, gamma camera; echo, echocardiography; MRI, magnetic resonance imaging; RNV, radionuclide ventriculography; EBT, electron beam tomography; XR, X-ray and EM, electromechanical.

**Table 4** Classes of indication for imaging techniques in the patient with stable left ventricular dysfunction as a result of ischaemic heart disease

<table>
<thead>
<tr>
<th>Echo</th>
<th>MPS</th>
<th>PET</th>
<th>RNV</th>
<th>MRI</th>
<th>Angio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>S</td>
<td>R+S</td>
<td>G</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>R&lt;nav&gt;1&lt;/nav&gt;</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Angina (no HF)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>MILD/mod HF (with angina)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MILD/mod HF (no angina)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Severe HF</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

See Table 3 for abbreviations. HF, heart failure; R, rest; S, stress and G, gated.
Imaging techniques for the assessment of myocardial hibernation

Writing group
Underwood SR (co-chair), Bax JJ (co-chair), vom Dahl J, Henein MY, Knutti J, van Rossum AC, Schwarz ER, Vanoverschelde JL, van der Wall EE, Wijns W.

Advisory group

References

Fig. 6 Simplified clinical algorithm for the use of imaging techniques in selecting therapy in the patient thought to have ischaemic left ventricular systolic dysfunction and heart failure.
830 S.R. Underwood et al.


63. Assessment of residual myocardial viability in regions with chronic electrocardiographic Q-wave infarction. *Am Heart J* 2002;144:865–869.


Imaging techniques for the assessment of myocardial hibernation


259. Meluzin J, Cerny J, Frelich M et al. Prognostic value of the amount of dysfunctional but viable myocardium in revascularized patients


