Radionuclide imaging in ischaemic heart failure

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Introduction or background: Many tests are available for the investigation of patients with heart failure. The identification of the underlying aetiology of ventricular dysfunction is crucial as early treatment may limit or even reverse myocardial abnormalities.

Sources of data: This article describes cardiac radionuclide imaging techniques and their applications in ischaemic ventricular dysfunction. Evidence for the role of these techniques is summarized with particular reference to current guidelines.

Areas of agreement: Both positron emission tomography (PET) and single photon emission computed tomography (SPECT) techniques are widely validated for the detection of myocardial viability and their use is recommended in both national and international guidelines.

Areas of controversy: Although assessments of ventricular phase and myocardial innervation hold promise for the stratification of patients to cardiac resynchronization therapy, the poor performance of echocardiographic predictors of response in the recently published PROSPECT trial suggest that these techniques face a tough challenge.

Growing points: The use of integrated multimodality imaging techniques such as PET/computed tomography to assess for ischaemic causes of left ventricular dysfunction is an area that is currently under investigation, as is the role of nuclear techniques in the assessment of stem cell retention, distribution and function when used in patients with heart failure.

Areas timely for developing research: Ongoing developments in radionuclide molecular imaging for assessment of angiogenesis, apoptosis and interstitial alterations during cardiac remodeling may have important implications for the prognosis and treatment of patients with heart failure.

Keywords: myocardial perfusion scintigraphy/coronary artery disease
**Introduction**

Heart failure remains a major cause of morbidity and mortality in the Western world, with coronary artery disease (CAD) accounting for around 70% of cases.\(^1\) The identification of the underlying aetiology of heart failure is paramount as prompt treatment may limit progression of myocardial injury and even reverse ventricular dysfunction. Heart failure has been traditionally thought of as an impairment of systolic function. More recently, however, the concept of heart failure with preserved ejection fraction has been recognized. The role of cardiac radionuclide imaging in stable coronary artery disease and acute coronary syndromes has been dealt with previously.\(^2\) This review focuses on the use of cardiac radionuclide imaging in the investigation of systolic ventricular dysfunction of ischaemic aetiology, with emphasis on single photon emission computed tomography (SPECT) myocardial perfusion scintigraphy (MPS), positron emission tomography (PET) and radionuclide ventriculography (RNV). Other tracers, including iodine-123 metaiodobenzylguanidine (MIBG) and beta-methyl-iodophenylpentadecanoic acid (BMIPP), will also be reviewed briefly.

**The clinical setting**

Approximately 15 million people suffer from heart failure in Europe\(^1\) with CAD the cause in around 70%. The management of patients with heart failure has improved significantly over the last decade and this contributes, in part, to the increasing prevalence of the condition. Despite this, median survival is only around 4 years. Heart failure may be diagnosed in the presence of typical symptoms and signs in addition to objective evidence of a structural or functional abnormality of the heart at rest.\(^1\) The latter condition is most commonly investigated through the use of laboratory tests (natriuretic peptides, troponins) and non-invasive imaging. Transthoracic echocardiography is generally considered the most useful test for the evaluation of systolic and diastolic dysfunction\(^1\) and is considered mandatory in those with suspected heart failure. Radionuclide and cardiovascular magnetic resonance (CMR) imaging are also used frequently, particularly for the evaluation of myocardial perfusion and function. As with all non-invasive testing, clinical utility relies on the ability of the test to allow stratification of patients to different diagnoses and management strategies. Current forms of treatment for those with heart failure include: medical treatment, device therapy, heart transplantation and revascularization.
Radionuclide imaging plays a pivotal role in the identification of myocardial ischaemia as underlying cause of heart failure as its treatment may improve symptoms, ventricular function and, importantly, long-term outcome. The latter is related to the severity of the ischaemic burden as well as the degree of left ventricular (LV) dysfunction. These parameters are readily measured by radionuclide imaging techniques using either single-photon or positron emitting radiotracers. In certain circumstances, serial monitoring of LV function may be desired, with RNV a suitable option in this case.

**Diagnosis using radionuclide techniques**

**Myocardial perfusion scintigraphy**

The principles of MPS have been described in the first part of this review. Beyond the detection of perfusion abnormalities that correspond to inducible ischaemia and myocardial infarction, ECG gating of the resting tomograms allows calculation of LV end systolic and diastolic volumes and thus ejection fraction. The diagnosis of heart failure may therefore be made whilst investigating the possibility of obstructive CAD. Gated MPS is classed as an appropriate indication for the assessment of LV function where echocardiography is non-diagnostic, although RNV is probably more appropriate if information on myocardial perfusion is not required. LV ejection fraction can also be obtained by PET. Fluorine-18 fluorodeoxyglucose (FDG) is the preferred tracer in this setting, and compares well with magnetic resonance imaging (MRI) for the calculation of LV function.

**Radionuclide ventriculography**

Assessment of LV systolic and diastolic dysfunction can be made by equilibrium RNV. Red blood cells are labelled with technetium-99 m pertechnate and reinjected into the patient. Once these have equilibrated within the blood pool, the LV is imaged in static planar anterior and left anterior oblique projections. Counts within the LV blood pool are directly proportional to the volume of blood within it and, through the use of ECG gating, LV volumes may be calculated at different phases of the cardiac cycle. Comparison of end-systolic and end-diastolic volumes allows the calculation of LV ejection fraction. This is a highly accurate and reproducible technique. In addition to measures of global ventricular function, timing of regional contraction is possible on both planar and SPECT equilibrium RNV.
Analysis of ventricular phase may have important implications for cardiac resynchronization therapy (CRT) and is discussed in the relevant section below. The inaccuracies inherent to the planar technique may be resolved through the use of SPECT imaging, which allows three-dimensional assessment of the LV blood pool. Although this relatively new technique is not yet in routine clinical use, ventricular functional parameters obtained from SPECT RNV compare well with the MRI. SPECT RNV is the subject of ongoing trials but promises high accuracy and reproducibility. Although used less frequently, RNV may be performed using a first pass technique. For this study, the radiotracer is injected as a bolus and images are acquired immediately as the bolus passes through the heart. Whilst more technically challenging, this method allows very accurate assessment of both left and, importantly, right ventricular function. Guidelines for the use of RNV are included in Table 1.

### Heart failure of ischaemic aetiology

In patients with heart failure, it is imperative that reversible causes of LV dysfunction be identified and treated. Distinction of patients who stand to benefit from revascularization remains one of the most challenging aspects of cardiology today. The concepts of myocardial viability, stunning and hibernation discussed below underpin this distinction and are crucial in deciding management strategy in patients with heart failure.
Myocardial viability, stunning and hibernation

The term ‘myocardial viability’ is often used in a broad and sometimes confusing context as an interchangeable term for myocardium that recovers function after revascularization. In fact, viability relates simply to the presence of living myocardium, without reference to the state of perfusion, metabolism or function. In this way, infarcted tissue is considered non-viable and any non-infarcted myocardium will be viable. Beyond this simple classification, there exist other states where myocardium may be viable but dysfunctional. These are referred to as ‘stunning’ and ‘hibernation’, and it is the identification of these areas that will determine the management strategy in a patient with LV dysfunction.

Stunned myocardium

Stunning refers to the phenomenon of regional contractile impairment, usually as a result of an ischaemic insult, which persists for hours or weeks even after restoration of normal coronary blood flow. There is therefore a mismatch of perfusion and function, with the former being normal (or near normal) but the latter impaired. Such a phenomenon is often seen after restoration of coronary blood flow following acute myocardial infarction. However, stunning may occur as a result of exercise-induced ischaemia (in the presence of high-grade coronary stenosis) or after cardioplegic arrest during open-heart surgery. Recovery of myocardial function is spontaneous providing that myocardial perfusion remains normal.

Hibernating myocardium

Hibernation, in its original definition, refers to dysfunctional myocardium that is in a state of metabolic down-regulation in response to reduced perfusion. However, resting flow in hibernating myocardial segments may not be decreased to the extent that would account for the degree of cardiac dysfunction. In most cases, there is impairment of coronary flow reserve, with reduction of resting blood flow seen in only the most advanced cases. Hibernation may, therefore, represent a spectrum with chronic repetitive stunning showing normal or near normal resting blood flow and impaired flow reserve at one end and reduced resting blood flow at the other. Accordingly, hibernating myocardium can be defined as viable but dysfunctional myocardium susceptible to myocardial ischaemia. Although the exact underlying phenomena in hibernation remain unclear, alteration of structural proteins and metabolism, disorganization of the cytoskeleton, loss of myofilaments, glycogen vacuoles and sarcomeric instability may all result
...from impairment of myocardial perfusion and lead to myocardial dysfunction (Fig. 1).\textsuperscript{14}

**Clinical relevance**

The relative merits of mechanical revascularization compared with medical therapy have been demonstrated mostly in retrospective studies. Many exclude patients with severe LV dysfunction where hibernation is arguably most relevant and fail to distinguish whether the dominant symptom is angina or heart failure. The exact prevalence of myocardial hibernation is unclear, although up to 60\% of dysfunctional segments may improve after revascularization.\textsuperscript{14} The degree to which global LV function improves is related to the extent of hibernating myocardium,\textsuperscript{15} although recovery may be prolonged for up to 14 months after revascularization depending on the severity of underlying ultrastructural changes.\textsuperscript{16} Usually a minimum of at least four viable segments in a 16-segment model of the LV is advised as a cutoff value to predict the improvement in the LV ejection fraction,\textsuperscript{17} although six\textsuperscript{15} or even seven\textsuperscript{18} segments may be more appropriate. As well as improvements in ejection fraction, reverse LV remodelling may be seen when hibernating myocardium is...
revascularized, with reductions in end-diastolic and systolic volumes and restoration of LV geometry after revascularization. Furthermore, the extent of hibernation predicts the likelihood of symptomatic improvement after revascularization. A retrospective meta-analysis suggests that revascularization of hibernating segments carries an improved prognosis, with at least a 50% reduction in mortality compared with patients without evidence of hibernation and a 4-fold reduction compared with those with hibernation treated medically. Cardiac death and acute ischaemic events represent separate prognostic outcomes, with the former related mainly to the severity of LV dysfunction and the latter to the percentage of viable myocardium that is ischaemic. In patients with large areas of infarction, an ischaemic burden that might be considered rather small in a normal heart may constitute a large percentage of the remaining viable myocardium and it is this value that predicts those who benefit from revascularization. A survival benefit may be seen after revascularization even in the absence of a meaningful improvement in ejection fraction possibly because restoration of normal myocardial perfusion reduces or even abolishes the ischaemic substrate and hence the likelihood of acute ischaemic events. It should be noted that the medical therapy offered in the retrospective studies to date can no longer be considered current. Indeed, a review of the more recent literature suggested that patients receiving optimal, current medical therapy have a similar annual mortality irrespective of the presence of viability. It is for this reason that prospective studies comparing current medical therapy and revascularization techniques are so keenly awaited.

Non-invasive imaging for detection of viability and hibernation

Several radionuclide techniques have been developed for assessment of myocardial viability and hibernation using PET or SPECT. Current guidelines for the use of PET and SPECT for the investigation of patients with heart failure are summarized in Table 1. Dobutamine stress echocardiography (DSE) is a widely validated alternative with sensitivity and specificity of 78% for the detection of hibernating myocardium. DSE suffers from operator dependence but lacks associated radiation and the licensing issues that are a feature of nuclear investigations. CMR can identify myocardial scarring through its uptake of gadolinium contrast agents on delayed acquisition. The transmural extent of gadolinium enhancement, along with detection of associated LV wall motion and thickening abnormalities, allows very accurate identification of myocardial scarring, with the remaining myocardium
viable by implication. Although CMR has a sensitivity and specificity of 94 and 87%, respectively, for prediction of functional recovery of the myocardium after revascularization, its widespread use is constrained by high cost, low availability and operator dependence. Furthermore, the higher prevalence of renal dysfunction in those with heart failure increases the risk of nephrogenic systemic fibrosis after gadolinium administration. Each technique makes use of different physiological processes to image myocardial viability and can delineate irreversibly scarred from dysfunctional but viable myocardium with varying sensitivity and specificity. Myocardial perfusion, cell membrane integrity, mitochondrial function, glucose utilization and contractile reserve may all be assessed and their presence or absence relates to the severity of ultrastructural damage at the myocyte level.

Positron emission tomography
PET has been considered for many years as the ‘gold standard’ for assessment of myocardial viability using metabolic tracers. The high-energy photons released from the annihilation of positrons confer a spatial resolution superior to SPECT. Furthermore, combination with attenuation correction allows quantitative analysis of regional myocardial blood flow and metabolism. The advantage of PET is the ability to label naturally occurring elements in the body such as carbon, oxygen and nitrogen (Table 2). For assessment of myocardial perfusion, oxygen-15 water, nitrogen-13 ammonia (NH₃) and rubidium-82 chloride can be used. Currently available tracers for the assessment of myocardial metabolism are the glucose analogue FDG and less commonly carbon-11 acetate. NH₃/FDG-PET or rubidium-82/FDG-PET are the most common combinations for the detection of hibernation in clinical practice. Dysfunctional myocardial segments with higher FDG uptake compared with that of NH₃ or rubidium-82 (mismatch between and perfusion and metabolism) represent hibernating myocardium whilst reduction on both perfusion and metabolism suggests the presence of scarring. In cases of myocardial stunning, perfusion is normal or almost normal whilst the FDG uptake is variable. The sensitivity and specificity of FDG-PET for

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Physical half-life</th>
<th>Radiopharmaceutical</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>^82Rb</td>
<td>76 s</td>
<td>Rubidium chloride</td>
<td>Blood flow, membrane integrity</td>
</tr>
<tr>
<td>^15O</td>
<td>120 s</td>
<td>Water</td>
<td>Blood flow, perfusable tissue index</td>
</tr>
<tr>
<td>^13N</td>
<td>10 min</td>
<td>Ammonia</td>
<td>Blood flow</td>
</tr>
<tr>
<td>^18F</td>
<td>110 min</td>
<td>Deoxyglucose (FDG)</td>
<td>Glucose metabolism</td>
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segmental recovery of hibernating myocardium after revascularization are 89 and 57%, respectively, with positive and negative predictive values of 73 and 90%, respectively.\textsuperscript{15}

The major disadvantages of PET are its limited availability and cost. For instance, although oxygen-15 water has a myocardial extraction fraction of virtually 100% and is hence an excellent tracer of myocardial perfusion, it must be manufactured using an on-site cyclotron because of its very short half-life. Nitrogen-13 NH\textsubscript{3} is also difficult to access unless there is on-site cyclotron. Thus, in clinical practice, rubidium-82 is the most widely used PET radiotracer for assessment of myocardial perfusion. A rubidium generator lasts for 1 month but it is relatively expensive (approximately €30 000). To overcome the limitations related to PET perfusion tracers, some centres have adopted a hybrid (SPECT/PET) approach combining FDG-PET with a SPECT perfusion tracer such as thallium-201 or technetium-99 m. Although conceptually this is an interesting combination,\textsuperscript{25} there are technical issues regarding the comparison of PET and SPECT images.

**Single photon emission computed tomography tracers**

SPECT is a well-established and widely available technique. Thallium-201 is not only a perfusion agent but also a tracer of myocardial viability due to the reliance of tracer uptake on both myocardial blood flow and sarcolemmal integrity. It has therefore been used widely for identifying myocardial hibernation. A common threshold for defining clinically significant viability is $\geq 50\%$ of maximal myocardial uptake, although the best threshold may be higher. As thallium redistribution may be slow or incomplete in regions of reduced perfusion, the usual stress/redistribution protocol can underestimate myocardial viability and additional steps may be required. These include the use of sublingual nitrates prior to resting assessment where a severe defect is seen on stress images, late redistribution imaging at 8–72 h after stress injection, reinjection of tracer at rest after redistribution imaging and a resting injection on a separate day with both early and delayed imaging.

Technetium-99 m sestamibi and tetrofosmin have also been used for the detection of viable and hibernating myocardium. In theory these tracers may underestimate viability in areas with reduced resting perfusion because they do not redistribute and cannot thus allow independent distinction of perfusion and viability. Some studies have therefore found thallium MPS to be a more sensitive test for the assessment of viability.\textsuperscript{26} However, the use of sublingual nitrates improves resting perfusion and thus the detection of myocardial viability using technetium tracers. For this reason and unless contraindicated, sublingual...
nitrates should be administered prior to resting tracer injection in all patients with severe defects on stress acquisitions. Whichever tracer is used, SPECT assessments have generally higher sensitivity but poorer specificity when compared with DSE for the detection of myocardial viability. The higher sensitivity of SPECT is likely to be due to the reliance of tracer uptake on myocyte membrane integrity, which may be preserved even after loss of myocyte contractile reserve. The use of a ≥50% threshold of maximal myocardial uptake to identify viability may contribute to the poorer specificity. A myocardial segment with 60% of the maximal myocardial uptake will be classified as viable even though the reduction may be due to partial thickness myocardial damage that will not recover after revascularization.

An important advantage of using sestamibi or tetrofosmin SPECT is the ability to perform ECG gating and thus assess ventricular function. Comparative studies between MRI and gated SPECT have shown good agreement for myocardial wall motion and thickening where myocardial tracer uptake is present.27 Since detection of hibernation requires knowledge of viability, perfusion and function, ECG-gated SPECT is ideally suited for assessment of patients with heart failure by providing information on all these parameters in a single study. Pooled data analysis from studies using thallium-201 and technetium-99 m reveals that the sensitivity and specificity of SPECT MPS for segmental recovery of hibernating myocardium after revascularization are 89 and 68%, respectively, with positive and negative predictive values of 73 and 84%, respectively.15

Other tracers and emerging techniques

Although the myocardium represents the focus of most investigations in heart failure, there is growing evidence that other aspects of cardiac physiology may be of relevance. In particular, assessment of myocardial sympathetic innervation using the noradrenaline analogue iodine-123 metaiodobenzylguanidine (MIBG) has become a subject of substantial research interest. As sympathetic nerves supplying the heart are more sensitive to ischaemia than myocardium,28 periods of ischaemia insufficient to cause myocardial necrosis may nonetheless lead to sympathetic nerve death in the territory of the compromised coronary artery and thus heterogeneity of global myocardial sympathetic distribution. Myocardium that is viable but sympathetically denervated has a greater propensity for arrhythmogenesis.29 Assessment of regional myocardial sympathetic supply using MIBG may therefore help in the selection of patients for implantable cardiac defibrillators. A more global approach is to assess the total myocardial sympathetic supply
through planar MIBG imaging. Total MIBG uptake within the heart may be compared with a reference area, usually the mediastinum, to calculate the heart–mediastinum ratio (HMR). This is a measure of the integrity of the cardiac sympathetic nervous system and a low HMR indicates poor uptake of MIBG and diminished total cardiac sympathetic coverage. If images are acquired soon after injection of MIBG and then again several hours later, the comparison of HMR between the early and delayed images (washout rate) gives information on the function of the sympathetic nerves of the heart. A high washout rate indicates elevated spillover of NA from presynaptic nerve terminals and thus elevated sympathetic nerve activity. Elevated sympathetic tone in heart failure has been suggested by the measurement of plasma and coronary sinus noradrenaline levels, heart rate variability and muscle sympathetic nerve activity. Low HMR and high washout rates correlate with a poorer prognosis in heart failure. The recently completed multicentre ADMIRE-HF trial demonstrated that patients with HMR < 1.6 demonstrated higher mortality than those above this threshold. Interestingly, those with HMR < 1.2 were more likely to die as a result of heart failure progression whereas those with HMR 1.2–1.6 had a greater likelihood of arrhythmic death. These parameters may be useful in predicting response to CRT and thus allow stratification of patients to either conservative or interventional management strategies. For example, lower HMR prior to CRT implantation has been shown to correlate with non-response; HMR may also improve in responders, suggesting a beneficial effect of CRT on myocardial sympathetic nerves. Larger trials are underway to evaluate fully the role of MIBG in this setting. Cardiac sympathetic and parasympathetic receptors can also be assessed by positron-emitting radiotracers. These include the catecholamine analogue [11C]hydroxyephedrine and tracers for the measurement of β-adrenoceptor and muscarinic receptors. Like the studies performed with MIBG, PET imaging of myocardial neural function and innervation has been shown to have strong prognostic value in patients with heart failure. However, the cost and availability of PET tracers are important limitations hampering their widespread use in clinical practice.

Fatty acid metabolism is another parameter that can be assessed by nuclear techniques. Fatty acids serve as the primary myocardial energy source but, during periods of ischaemia, stores are quickly exhausted and myocardial metabolism switches to glucose. This switch may persist for several hours, even after restoration of normal myocardial perfusion. Myocardial metabolism may be imaged through the use of radiolabelled fatty acid analogues, of which the most widely studied is iodine-123 BMIPP. This tracer is taken up by metabolically active myocardium but not by infarcted tissue or myocytes that have switched to
glucose as their primary energy source. BMIPP imaging therefore offers the opportunity to detect myocardial ischaemia even after it has resolved, a phenomenon referred to as ‘ischaemic memory’. In those with chronic CAD, myocardial segments demonstrating inducible ischaemia may have larger resting BMIPP defects compared with resting thallium-201 images, suggesting that the metabolic abnormality may be more severe than would be expected from the defect in perfusion. Uptake within areas of infarcted myocardium is similar for both BMIPP and thallium-201. In patients with chronic CAD and depressed LV function, the presence and extent of discordant BMIPP uptake compared with both thallium-201 and technetium-99m labelled agents is a good predictor of functional recovery after revascularization. BMIPP and MIBG, when used in tandem, may have particular value in the diagnosis of vasospastic angina as metabolic and neuronal changes persist even though the ischaemic insults are transient.

Assessment of myocyte apoptosis using 99mTc annexin 5 is another technique that may find use in the future. This radiotracer has been used to identify early rejection in heart transplant recipients as well as in patients with progressive worsening of symptoms in the setting of dilated cardiomyopathy and may be useful in the identification of patients with accelerated myocardial cell loss. Other biological targets for molecular imaging in chronic dysfunctional myocardium may be extracellular matrix activation, collagen deposition or inflammation. Imaging of matrix metalloproteinase activity may come to play an important role in defining the process of LV remodelling after myocardial infarction. A further emerging application of PET centres on the use of reporter genes and labelled reporter probes for non-invasive imaging of transgene expression. This technique is based on the vector-mediated transfer of genes that translate into protein products such as enzymes or receptors that can be targeted by radiotracers. Accumulation of tracers thus indirectly reflects gene expression in target tissue. Several experimental studies have reported proof of this principle for cardiac imaging. Stem cell transplantation is another approach that holds potential promise for treatment of ischemic heart disease. In clinical studies, changes in myocardial perfusion, viability and perfusion are assessed with SPECT and PET imaging, thus allowing evaluation of response to treatment. Finally, multimodality imaging in the form of PET/CT or SPECT/CT may be of special value in chronic LV dysfunction by incorporating morphological data that complement the physiological or biological information obtained by PET or SPECT imaging alone. The precise role of multimodality imaging in this setting is currently under investigation.
Radionuclide imaging and cardiac resynchronization therapy

Background

ESC guidelines recommend CRT as a class I indication to reduce morbidity and mortality in symptomatic (NYHA III or IV) patients who are symptomatic despite optimal medical therapy with LV ejection fraction $\leq 35\%$ and prolonged QRS interval ($\geq 120$ ms).\textsuperscript{1} In this population, delayed electrical activation and impaired excitation–contraction coupling results in a dispersion of regional mechanical activation. This results in dyssynchronous contraction both within the LV (intra-ventricular dyssynchrony) and between the left and right ventricles (interventricular dysynchrony). These phenomena are associated with pre-systolic mitral valve regurgitation, decreased LV diastolic filling time, reduced LV contractility and occasionally with septal wall dyskinesia. Biventricular pacing results in resynchronization of ventricular contraction, which may optimize LV filling, reduce functional mitral regurgitation and reduce or even reverse LV remodelling. These effects may thus improve LV function and hence reduce the symptoms of heart failure and improve exercise capacity. Current data suggest that around one-third of patients who meet the criteria for CRT fail to respond symptomatically. As the insertion of CRT devices, whether or not combined with implantable cardiac defibrillator, is costly and not without risk, considerable effort has been expended on the non-invasive prediction of patients who stand to benefit.

Role of radionuclide imaging

Although widely measured in patients with heart failure, echocardiographic parameters of dyssynchrony are not predictive of response to CRT.\textsuperscript{47} The presence of myocardial scarring, particularly in the region in which the LV pacing lead is placed, is an important determinant of the success of CRT. Those with larger areas of myocardial scarring measured using SPECT radiotracers are less likely to respond to CRT,\textsuperscript{48} particularly when the scarring is posterolateral.\textsuperscript{49} Similar findings have been found with FDG-PET.\textsuperscript{50} Assessment of myocardial scarring is thus useful prior to decision to install a CRT device as it may help to predict the probable success of the procedure. Although used less often in clinical studies, both SPECT MPS and RNV may be used to assess changes in ventricular dimensions and function and thus gauge LV remodelling after heart failure therapy. Amongst other non-invasive techniques, interest is focused currently on phase analysis of equilibrium RNV. Both planar and SPECT techniques are able to
evaluate left and right ventricular phase, a variable that represents the timing of ventricular contraction. Phase analysis allows quantification of the temporal sequence of systolic ventricular wall motion and is displayed as a colour-coded histogram in which the $y$-axis represents the number of pixels and $x$-axis the phase angle. The latter corresponds to the relative sequence and pattern of ventricular contraction of each pixel within the LV blood pool. The mean phase angle is used to evaluate regional synchrony. The difference between mean phase angles of the right and LVs can be used to determine interventricular synchrony. The standard deviation of the phase angle indicates the spread of different phase angles within a ventricle and is thus a marker of intraventricular synchrony. Three-dimensional imaging reduces the effects of overlap and obviates ventricular separation required by planar imaging, thus making SPECT RNV intuitively more advantageous. However, the processing software is more complicated and needs rigorous validation. Both planar and SPECT RNV have been tested for predicting both response to CRT\textsuperscript{51} and likelihood of cardiac death\textsuperscript{52} in heart failure patients, but their exact role in clinical practice is still under investigation. Phase analysis can also be performed on images obtained from standard gated SPECT MPS studies.\textsuperscript{53,54} This has the potential to increase the usefulness of the test in those with heart failure and may, like RNV, allow prediction of those who would benefit from CRT.

**Conclusion**

Cardiac radionuclide imaging has a wide variety of applications in heart failure. As for the investigation of CAD, experience with these techniques can be measured over decades and evidence supports their integration into diagnostic strategies for the investigation of heart failure. PET and SPECT techniques are widely validated for both the diagnosis of obstructive CAD as a cause for LV dysfunction and the identification of hibernating myocardium requiring revascularization on prognostic grounds. For this reason, the use of these techniques is heavily embedded in US and European guidelines for the management of patients with heart failure. Beyond myocardial perfusion, radionuclide techniques can be used to assess left and right ventricular function, myocardial innervation and metabolism, and response to heart failure therapy. Cardiac radionuclide imaging therefore comprises a broad suite of techniques that have high clinical utility in patients with heart failure.
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