

Multimodality imaging of myocardial viability: an expert consensus document from the European Association of Cardiovascular Imaging (EACVI)

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In clinical decision making, myocardial viability is defined as myocardium in acute or chronic coronary artery disease and other conditions with contractile dysfunction but maintained metabolic and electrical function, having the potential to improve dysfunction upon revascularization or other therapy. Several pathophysiological conditions may coexist to explain this phenomenon. Cardiac imaging may allow identification of myocardial viability through different principles, with the purpose of prediction of therapeutic response and selection for treatment. This expert consensus document reviews current insight into the underlying pathophysiology and available methods for assessing viability. In particular the document reviews contemporary viability imaging techniques, including stress echocardiography, single photon emission computed tomography, positron emission tomography, cardiovascular magnetic resonance, and computed tomography and provides clinical recommendations for how to standardize these methods in terms of acquisition and interpretation. Finally, it presents clinical scenarios where viability assessment is clinically useful.

Keywords

myocardial viability • review • multimodality imaging • stress echocardiography • cardiac magnetic resonance • SPECT • PET

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Introduction

Loss of myocytes due to myocardial necrosis in coronary artery disease remains the leading cause of heart failure. In this setting, identification of the extent and severity of myocyte loss by cardiac imaging and, conversely the identification of myocardial viability are clinically useful for decision making and selection of therapeutic strategies for patients with ischaemic left ventricular (LV) dysfunction. Indeed, myocardial viability assessments are widely used in routine practice in a range of clinical scenarios. Most reviews¹ and recommendations regarding the imaging assessment of myocardial viability were produced in the 1990 and 2000s. However, since these reports, important technical progress has been made and new scientific results have been published. Furthermore, the concept of myocardial viability has evolved from coronary artery disease with the purpose of myocardial revascularization, to other myocardial diseases including valvular heart disease and non-ischaemic cardiomyopathies where it is used to guide other therapeutic options such as cardiac resynchronization therapy (CRT) and dedicated electrical interventions.

Aim of the report

The purpose of this consensus document is to provide a comprehensive and critical review of current indications and techniques for myocardial viability assessment. We aim to revisit the current state of the art viability techniques and to review recommendations on how viability testing should be performed and interpreted and when these techniques might be useful in current clinical practice.

Pathophysiology of myocardial viability

The pathophysiology of myocardial viability has been reviewed in detail elsewhere.^{2–5} Myocardial metabolism is predominantly aerobic with acute ischaemia leading to rapid cessation of contractile function. The concept of “myocardial viability” was established in the early 1970s following the clinical observation that chronically dysfunctional myocardium in stable coronary artery disease, may sometimes partially or completely recover contraction following coronary revascularization. It has been well identified that several distinct pathophysiological conditions may cause contractile dysfunction (Figure 1). Prolonged severe myocardial ischaemia generally induces irreversible myocardial necrosis and infarction. Acute myocardial ischaemia followed by reperfusion may lead to *myocardial stunning*, which is a sub-acute state of LV dysfunction persisting after acute ischaemia,⁶ when reperfusion has already occurred. Repeated episodes of stunning as well as chronic low flow may induce *Hibernating myocardium*⁷ a more advanced state of ischaemic dysfunction which is histologically characterized by myocellular dedifferentiation with loss of contractile proteins, change in gene expression, and alterations of myocardial metabolism with preferred use of glucose leading to glycogen accumulation in myocytes^{3,4} (Figure 2). Myocardial hibernation is a protective state of myocardial down-regulation, which may occur when the myocardium is exposed to repeated episodes of ischaemia and reperfusion, which are either not severe or long enough to cause myocellular necrosis. Importantly myocardial dysfunction in hibernating myocardium is potentially reversible upon revascularization.

Besides scar and stunning/hibernation, dysfunction in patients with chronic coronary artery disease may also be caused by other co-existent aetiologies which may be difficult to disentangle. Mechanical

Key point 1: chronic myocardial dysfunction in coronary artery disease may occur due to different conditions

- i. acute ischaemia,
- ii. stunning,
- iii. hibernation,
- iv. necrosis and replacement fibrosis,
- v. other confounding and coexisting diseases,
 - a. tethering/remodelling,
 - b. electromechanical dyssynchrony, and
 - c. myocyte loss or dysfunction due to other causes (i.e. inflammation, cardiomyopathy).

factors i.e. stretch due to global left ventricular remodelling⁸ or regional tethering⁹ from adjacent scarred regions may cause regional dysfunction. *Electromechanical dyssynchrony* due to disease in the electrical conduction system of the heart, either induced by ischaemia or unrelated factors, with ECG QRS widening and bundle branch block can also be a potential cause of segmental and global LV dysfunction¹⁰ and coexist in patients with CAD. Finally, contractile dysfunction may result from myocyte loss or dysfunction due to other causes such as inflammation, or *genetic, metabolic or toxic aetiologies*, superimposed or coexisting on the presence of ischaemic cardiomyopathy. This may be suspected particularly but not exclusively if dysfunction is generalized. When assessing patients with ischaemic cardiomyopathies it is also important to understand that these different pathophysiological states, rarely exist in a pure state, but often coexist and overlap in individual patients. Therefore, areas of irreversible scar and viable tissue may be mixed.

General pathophysiological principles underlying the imaging of viable and non-viable myocardium

Several pathophysiological principles and molecular targets may be used clinically to identify viable myocardium¹¹ (Figure 3). Viable myocytes are characterized by preserved energy conversion by mitochondria and maintained membrane function and action potentials. Therefore, myocardial viability may be identified by *preserved electrical activity*, for instance by endocardial surface potentials during electrophysiological mapping studies. ECG Q waves on the surface ECG are however relatively non-specific, relating more closely to the subendocardial extent rather than transmural of necrosis¹² and many myocardial segments with Q waves still demonstrate viability by other methods.¹³ *Membrane function* is explored by active uptake of 201Tl and *mitochondrial function* by retention of 99Tc-based tracers such as sestamibi and tetrofosmin. *Active contraction* is a definite marker of preserved myocyte viability. Dysfunctional segments at rest may or may not be viable and frequently require further assessment. Stunned and hibernating myocardium is characterized by reduced sensitivity of myofibrils to calcium, resulting in reduced mechanical efficiency at rest. This may be overcome when the intra-cellular calcium content increases, viable myocardium therefore has *preserved inotropic reserve*. These principles underlie the ability of dysfunctional viable

myocardium to improve contractility after premature beats, nitrate infusion and more commonly dobutamine stimulation. Another feature of viable myocardium is that *resting perfusion is generally preserved or only mildly reduced*, and that hibernating myocardium displays *preserved metabolism with metabolic preference for glucose over fatty acids in the fasting state*. These principles underlie the detection of myocardial viability using single photon emission computed tomography (SPECT) or positron emission tomography (PET) perfusion and metabolic imaging (such as combined NH₃ FDG PET). A final method for detecting myocardial viability is demonstrating the *absence of myocyte necrosis* and the *absence of replacement fibrotic tissue*. These principles underlie the detection of myocardial viability by late-gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR).

Key point 2: pathophysiological principles used to detect viable myocardium

- i. electrical activity (presence of local action potentials),
- ii. preserved membrane and mitochondrial function,
- iii. active contraction at rest or presence of contractile reserve (inotropic response, post-extrasystolic contraction),
- iv. preserved metabolism favouring glucose utilization, and
- v. absence of myocardial scar/extreme wall thinning or aneurysm.

Other approaches for viability assessment relate to the wall thickness¹⁴ and contraction patterns¹⁵ of myocardial segments. Chronic transmural scar is typically characterized by *wall thinning* leading to *aneurysm formation with dyskinesia* (i.e. bulging instead of contraction in systole). Many clinicians therefore use the presence of severe wall thinning (<6 mm wall thickness) and dyskinetic aneurysmal segmental movement as markers for non-viable myocardium. Whilst generally true, these thin segments may still very occasionally retain viable myocytes and therefore the potential for recovery following revascularization. Postsystolic (postejction) shortening, i.e. a myocardial deformation that occurs after aortic valve closure, has been also proposed as a marker of myocardial viability. Recent work demonstrated that it is however a purely passive phenomenon, resulting from the mechanical interaction of ischaemic with surrounding non-ischaemic segments, present in scar tissue¹⁶ and thus not specific for preserved viability¹⁷. Table 1 summarizes the different imaging techniques which use these pathophysiological principles.

Definitions of myocardial viability

Several different definitions have been used to describe myocardial viability and the terminology 'viable' and 'hibernating' is often used interchangeably and sometimes incorrectly.¹⁸ From a histopathologic and pathophysiological point of view, myocardial viability is presence of metabolically active myocytes *without myocardial infarction/scarring in dysfunctional myocardium*. At the macroscopic level that are interrogated by the currently available imaging methods, myocardial viability cannot be detected in single myocytes but only in ventricular wall segments which are composed of millions of functional myocyte groups. At this scale, viable functional, dysfunctional and necrotic myocytes may be admixed and therefore, from a clinical and imaging

point of view, myocardial viability has had different definitions. *Normal myocardium* with normal contractile function is considered by definition viable. It is metabolically active and exhibits contractile reserve in response to increased demand. Some imaging techniques may define dysfunctional myocardium *without infarction/scarring, with preserved perfusion and metabolism or with preserved inotropic response as viable*. However, viability was often defined as *reversibility of con-*

Key point 3: different definitions for myocardial viability have been used

- i. Actively contracting myocardium is considered viable (even if does not exclude admixture of small amounts of scar tissue).
- ii. Different definitions for viability in dysfunctional myocardium have been used, depending on the diagnostic tools:
 - a. metabolic viability (preserved metabolism and perfusion),
 - b. absence of infarction/scarring,
 - c. contractile response to inotropic stimulation, and
 - d. recovery of dysfunctional myocardium after revascularization.

tractile dysfunction after revascularization. These definitions are not necessarily interchangeable. In particular not all histologically or metabolically viable myocardium may be able to recover function, because functional improvement requires a large number of myocytes in a segment, and may not occur in subendocardial scars, or due to superimposed tethering, electromechanical dyssynchrony, excessive remodelling, incomplete revascularization, or coexisting cardiomyocyte dysfunction (i.e. a mixture of ischaemic and non-ischaemic causes of dysfunction). Furthermore, because of the dedifferentiation of cardiomyocytes, recovery of function is not immediate following revascularization, but may take up to 1 year to be completed. Therefore, sufficient time must be allowed to ascertain recovery of function. Moreover, recovery of function may be partial and thus more difficult to be detected, with higher inter-observer variability. *Stress-induced Ischaemia* is not *per se* a sign of myocardial viability and may often be observed in viable myocardium, however it remains an important assessment in dysfunction segments given its important role in the genesis of dysfunction and its potentially reversible nature.

Specific methods for viability detection

Echocardiography

Echocardiography plays an important role for detecting myocardial dysfunction in chronic coronary artery disease and for assessing improvement of such dysfunction after interventions. Assessment of myocardial viability is possible with stress echocardiography, which relies on demonstration of improvement of dysfunctional myocardium with moderate stress. In addition, myocardial ischaemia can be detected as deterioration of wall motion at high stress levels.

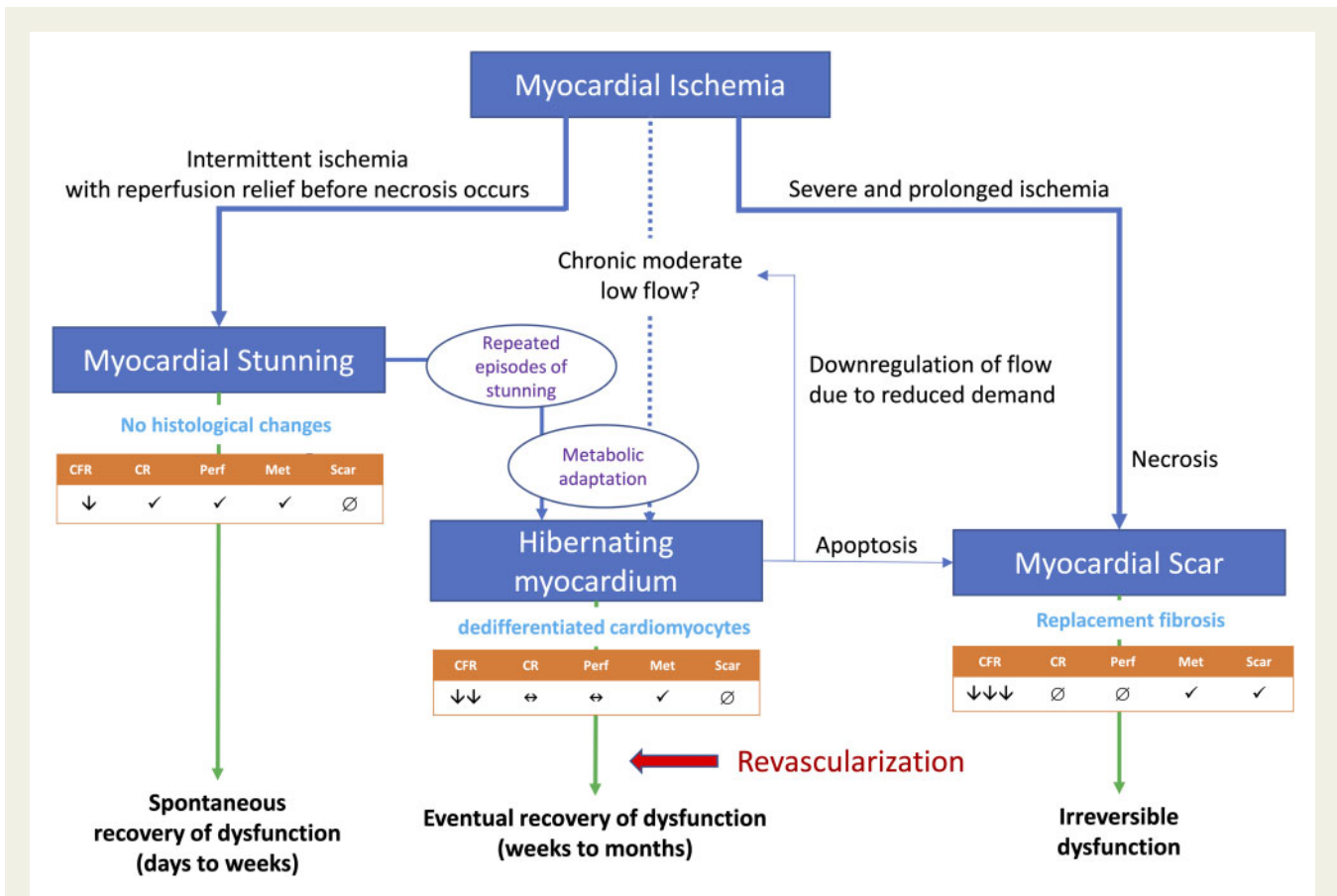


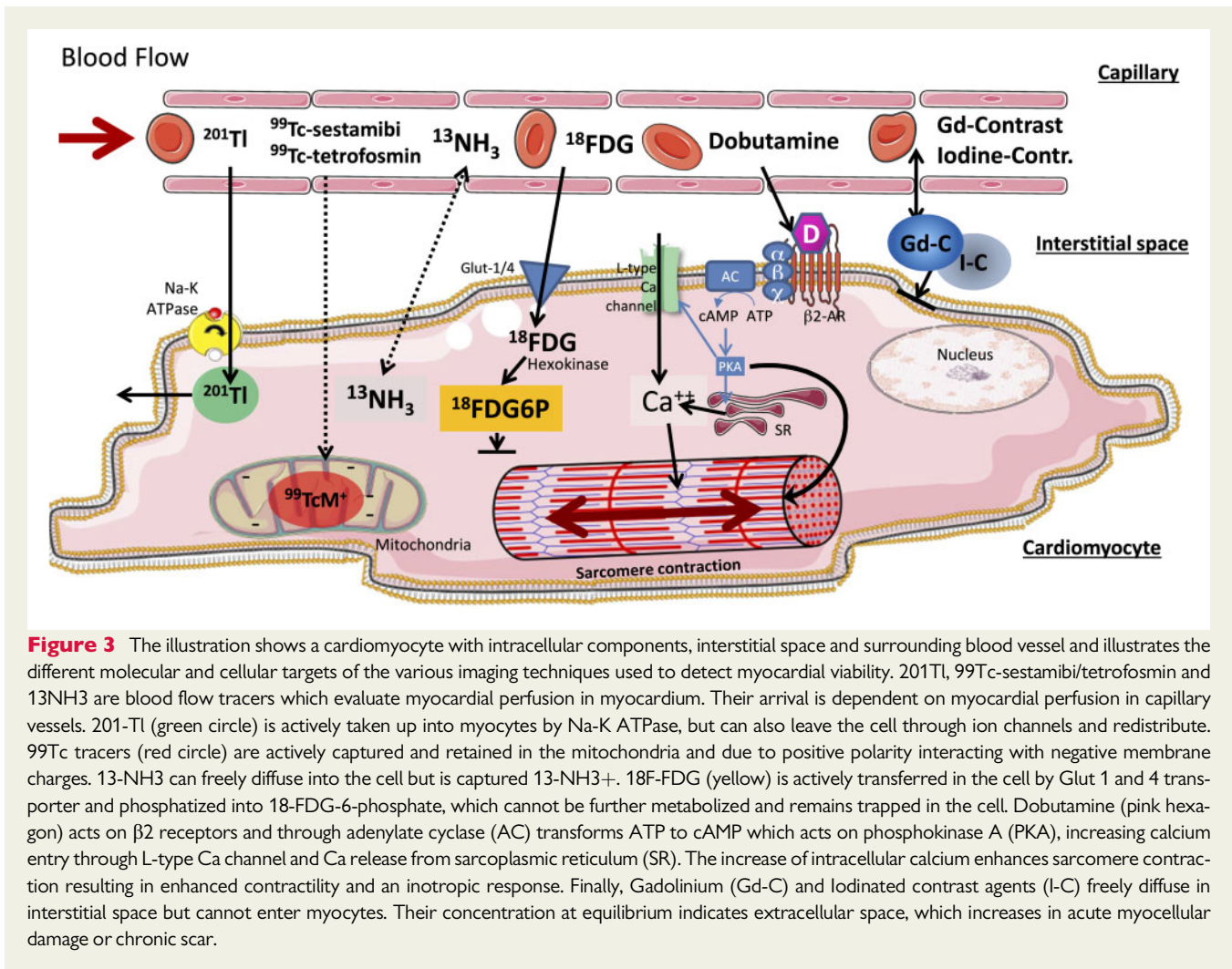
Figure 1 Pathophysiology of myocardial dysfunction in chronic coronary disease. The figure shows the postulated mechanism of development of different states of dysfunctional myocardium relation to the degrees of severity of myocardial ischaemia. Short intermittent ischaemia with reperfusion will induce myocardial stunning (transient post-ischaemic dysfunction) without necrosis, allowing spontaneous recovery within days to weeks. Repeated episodes of ischaemia and stunning as well as chronically reduced perfusion may induce metabolic and cellular adaptation leading to development of dedifferentiation of cardiomyocytes (hibernating myocardium). Hibernating myocardium retains the ability to recover function upon revascularization. Myocardial scar occurs in prolonged ischaemia due to necrosis, but also due to apoptosis when hibernating myocardium is not revascularized. Scar tissue represents irreversible damage without possible return of dysfunction after revascularization. Boxes below each state illustrate the pathophysiological responses seen at each stage. CFR, coronary flow reserve; CR, contractile reserve; MET, metabolism; PERF, perfusion; SCAR, scar or fibrosis; 3, present; ↔, equivocal response; x, absent. Adapted from Kloner *et al.*⁵ and Shah *et al.*²

Role of resting 2D and 3D and speckle tracking echocardiography

Because of its simplicity, availability, and low-cost, rest echocardiography is the principal method for detecting wall motion abnormalities due to myocardial infarction, stunning, or hibernation in patients with coronary artery disease and for evaluating the severity of systolic dysfunction. Serial echocardiography is used to evaluate disease progression and response to therapy by documenting changes in regional wall motion abnormalities and LV ejection fraction (LVEF) over time.

Simpson's biplane algorithm is recommended for the assessment of regional wall motion, and calculation of LV volumes and LVEF on two-dimensional echocardiography (2DE).¹⁹ When image quality is poor, LV chamber opacification by contrast media helps to improve wall motion characterization and evaluation of LV function. The 3D echocardiography (3DE) permits a more accurate and reproducible quantification of LV volumes and LVEF than 2DE without geometric

assumptions, which is particularly desirable in the presence of extensive wall motion abnormalities, or distorted shaped ventricles due to previous infarction(s).²⁰ The 3DE also avoids potential errors in LV regional wall motion assessment at rest and during stress inherent to 2DE, related to limited visualization of the myocardium, apical foreshortening, or oblique short-axis views.^{21–23} Therefore, it may be better suited than 2DE for follow-up studies, providing higher precision for the detection of progression in global dysfunction, as well as LV contractile recovery and reverse remodelling after coronary revascularization.^{19,20,24} The 2D and 3D speckle tracking (STE)-derived global longitudinal strain (GLS) can detect systolic dysfunction earlier than LVEF and provides additional prognostic information in a wide range of myocardial diseases.²⁵ GLS assessments may also be useful to follow improvements in global function after therapeutic interventions. Similarly, regional strains may be useful to better delineate wall motion abnormalities. Some authors have suggested that



detection of changes in wall motion abnormalities by 2DE.³¹ Wall motion is graded visually and semi quantitatively on a 4 grade Likert scale where 1 is normal, 2 hypokinesia, 3 akinesia, and 4 dyskinesia in 16 AHA segments. The scores of the different segments are summed. Inducible ischaemia is considered when wall motion scores degrade in two or more segments within the same coronary artery distribution region. These changes precede anginal symptoms and electrocardiographic ST-T changes in the ischaemic cascade. Viability³² assessments can be considered in segments that are dysfunctional (akinetic or dyskinetic) at rest. If such dysfunctional segments do not improve contractile function after pharmacological stimulation, they are considered non-viable (scar). By contrast, they are considered viable if they either improve persistently (sustained improvement) or first improve and then deteriorate (biphasic response due to superimposed ischaemia) during the stress test. Improvement of regional dysfunction is usually accompanied by improvements in global dysfunction, which may be assessed with GLS. If 2D stress echocardiography image quality is poor, intra-vascular contrast agents may be used to enhance LV chamber opacification.³³

Low-dose dobutamine is the preferred pharmacological stress agent for viability assessments as it has direct inotropic effects on

dysfunctional cardiomyocytes. At high doses, dobutamine has a predominant chronotropic effect leading to increases in oxygen demand, and potentially inducing ischaemia in myocardial regions supplied by a coronary artery with a critical stenosis.³⁴ This explains the biphasic response sometimes observed in viable segments with impaired perfusion. The standard high-dose protocol consists of a continuous intra-venous administration (by an infusion pump) of dobutamine, starting from $5 \mu\text{g/kg/min}$ and increasing to 10, 20, 30, and $40 \mu\text{g/kg/min}$ every 3 min.³¹ If the target heart rate is not obtained, the stress test can be completed by addition of atropine. For assessment of myocardial viability, a low-dose test starting at 2.5 or $5 \mu\text{g/kg/min}$ and increasing up to $10 \mu\text{g/kg/min}$ at 3–5 min intervals may be sufficient. Indeed a dose of $7.5 \mu\text{g/min/kg}$ was found to have the highest accuracy for predicting viable myocardium.³⁵ Sometimes, the definition of 'low dose' can vary, depending on the individual response of the patient to the drug. A heart rate increase of 10% compared with the basal value has been proposed as the best cut point for low-dose echocardiographic acquisition, independent of the quantity of administered dobutamine. Dobutamine is contraindicated in patients with ventricular arrhythmias, elevated basal blood pressure ($>180/100 \text{ mmHg}$), left ventricular outflow tract (LVOT) obstruction,

unstable angina, or recent myocardial infarction. Possible adverse events during dobutamine administration include prolonged ischaemia, asystole, symptomatic hypotension, dynamic LVOT obstruction, ventricular tachycardia, or ventricular fibrillation. During dobutamine stress echocardiography four different responses can be obtained (Figure 4): biphasic response (an improvement in systolic function during low-dose stress and subsequent deterioration at peak dose);³⁶ sustained improvement (gradual and sustained improvement along with drug infusion); deterioration; or no response.³¹ The biphasic response has high specificity (89%) and good sensibility (74%) in predicting functional recovery after coronary revascularization whilst the specificity is lower in cases of a sustained improvement (around 70%).^{37,38} The contractile response of viable myocardium in humans was shown to be inversely related to the extent of interstitial fibrosis³⁹ on histopathology. Observational studies have demonstrated that the presence of a contractile response predicts clinical and functional improvement after revascularization.^{40–42} The number of dysfunctional but viable segments per patient directly relates to the improvement in LVEF observed after revascularization, with patients requiring at least four viable segments for significant improvement of LVEF and heart failure symptoms to be detected. Presence of myocardial viability by low-dose dobutamine stress echocardiography has also demonstrated a reasonable correlation with other viability tests, including PET and 201-Tl scintigraphy.^{43,44}

Whilst dipyridamole stress echocardiography^{31,45} has similar diagnostic accuracy as dobutamine echocardiography for detection of ischaemia,^{46–49} the latter is clearly preferred for viability assessments. Indeed, the clinical evidence for dipyridamole stress echocardiography in assessing myocardial viability is poor compared with dobutamine. This is not unexpected as dipyridamole only acts as a vasodilator and does not have inotropic effects nor improve wall motion in dysfunctional segments.

Exercise echocardiography performed in an upright or semi-supine position is also widely used for ischaemia detection and, more recently also for evaluation of the severity of valvular disease. Compared with pharmacological stress, exercise echocardiography's main advantage is that it provides a more physiological stress response. Given the inotropic effect of exercise, low-level exercise tests (i.e. 50 W for 1–2 min or 25 W for 3 min) have also been proposed for contractile reserve assessment.⁵⁰ In a small series of 22 patients with chronic transmural myocardial infarction, a biphasic response during low-level exercise echocardiography was found to predict functional segmental recovery after coronary intervention with a sensitivity of 50% and a specificity of 84%.⁵¹ Low-level exercise echocardiography was found to induce a thickening in the centre of the ischaemic area similar to the extent of contractile reserve during standard dobutamine test and the accuracy in identifying contractile reserve by the two methods did not significantly differ.⁵⁰ However, given the small number of research studies in the area and the less predictable inotropic stimulation relative to dobutamine stress echocardiography, the latter should be used as the primary echocardiographic viability assessment.

Other echocardiographic approaches

Other echocardiographic approaches for evaluation of viability comprise tissue characterization by contrast echocardiography (MCE) and backscatter. MCE relies on ultrasound microbubbles close in size to red blood cells and allows measures of myocardial blood volume

Key point 4:

- i. High-dose dobutamine is the preferred echocardiographic method for the detection of both viability and ischaemia. Low-dose dobutamine is sufficient if knowledge of ischaemia is not required.
- ii. Dipyridamole and exercise echocardiography are better suited for the assessment of ischaemia than viability.
- iii. Ischaemia is considered present when at least two segments in the same coronary territory degrade by at least one-point with high-dose dobutamine.
- iv. Viability is considered present when at least two dysfunctional segments in the same coronary segments improve at low-dose dobutamine by at least one-point or present a biphasic response at high-dose dobutamine infusion.
- v. LV contrast opacification is encouraged in patients with suboptimal visualization of left ventricular walls.
- vi. Myocardial perfusion defects by MCE at rest may indicate no-reflow, which can be an indirect sign of absence of myocardial viability. However, this approach is limited by multiple artefacts.
- vii. Myocardial perfusion defects by MCE during stress may allow for improved detection of ischaemia compared with WM abnormalities alone.
- viii. LV scar may be indicated by wall thinning and hyper-reflective echo patterns, however the accuracy of this approach is influenced by machine settings.
- ix. The 3DE is more accurate to evaluate LVEF and recovery of dysfunction after revascularization than 2DE when patients have adequate image quality
- x. STE may help in interpreting improvements in regional or global dysfunction after therapy or during stress imaging

or myocardial blood velocity. These measurements correlate with microvascular density and capillary area as measures of microvascular integrity and inversely with collagen content.⁵² MCE has mostly been used to identify abnormal microvasculature, i.e. the no-reflow phenomenon in acute infarcts.^{53,54} Few studies have been performed in chronic MI, where MCE may be added to standard stress echocardiography to detect reduced myocardial perfusion during stress imaging.^{55,56} However, this technique remains technically challenging due to shadowing and attenuation, and whilst relatively sensitive (62–92%), is less specific than dobutamine⁵⁷ for predicting functional recovery after revascularization in akinetic segments.⁵⁸ MCE may allow the identification of scar tissue using enhanced ultrasound reflection in chronic MI similar to CMR.⁵⁹ Other echocardiographic approaches include detection of cyclic variations of the backscatter ultrasound signal as a representation of cardiomyocyte contraction.⁶⁰ The main disadvantage of this approach is its dependence on fibre orientation allowing evaluation of only those segments oriented perpendicularly to the ultrasound beam.

Advantages and limitations of echocardiography

The principal advantages of echocardiography for the assessment of viability are its widespread availability, low-cost and its high specificity for predicting functional recovery. The principal limitation is variable image quality, depending on the available acoustic windows which

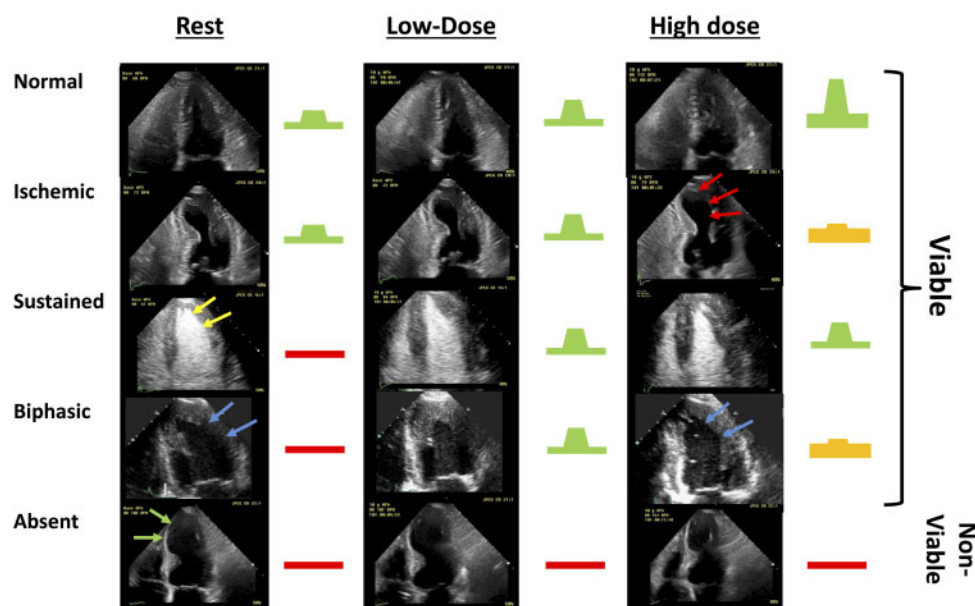


Figure 4 Detection of myocardial viability by dobutamine stress testing. Dobutamine response is classified according to five different contraction patterns. In viable myocardium without ischaemia, contractility increases progressively with increasing Dobutamine dose. In viable myocardium where there is flow-limiting epicardial coronary artery disease causing ischaemia, a biphasic response is seen with normal contractility at rest, an increase at low dose followed by a reduction in contractility at peak. Where myocardium is akinetic at rest (lower three rows), the response will determine whether the resting wall motion abnormality is due to a full thickness infarction (non-viable myocardium) or whether there is stunned or hibernating myocardium with or without ischaemia. See also [Supplementary data online, Movie S1](#).

can be particularly challenging in obese patients or those with pulmonary disease, although this may be overcome by the use of intra-cavity contrast agents.⁶¹ Other limitations include the subjective interpretation of wall motion scores and the consequent large inter-observer variability in assessment. However, this interpretation may be enhanced by deformation analysis using TVI or STE imaging.^{61,62} Finally, dobutamine stress echocardiography may have a relatively limited sensitivity for the detection of viable myocardium in particular in patients with very large ventricles and severe dysfunction or those with extremely severe coronary artery disease where extensive ischaemia may limit the inotropic response to dobutamine. Dobutamine may also have low sensitivity, albeit high specificity in total coronary occlusion, especially in akinetic segments.⁶³

Nuclear imaging

Nuclear imaging modalities (SPECT/PET) allow comprehensive assessment of patients with stable CAD and left ventricular dysfunction, who are being considered for revascularization, by evaluating complementary pathophysiological aspects of dysfunctional myocardium.^{11,64} In fact, they allow assessment of both the presence of inducible myocardial ischaemia and viability. SPECT mainly provides assessment of myocardial perfusion and by inference viability using tracers which are extracted by myocytes, proportional to flow and dependent upon cell integrity. PET is considered a gold-standard for

viability assessment, based on its ability to add specific metabolic information (i.e. glucose uptake) to that provided by perfusion imaging.

Single photon emission tomography

SPECT imaging provides reliable information on myocardial perfusion and to some extent cellular viability. Viability assessment can be performed either with ^{99m}Tc-sestamibi, a lipophilic cationic compound; ^{99m}Tc-tetrofosmin, a diphosphine agent; or with ²⁰¹thallium. Both sestamibi or tetrofosmin are transported passively into the myocyte and are sequestered within the mitochondria (Figure 3). Uptake requires negative transmembrane potentials of sarcolemmal and mitochondrial membranes. By contrast, Tl-201 mimics potassium, and is taken up actively into the myocyte through the Na-K-ATPase. The uptake and retention of all three tracers is dependent on regional blood flow and sarcolemmal membrane integrity (for thallium) or mitochondrial membrane integrity (for sestamibi and tetrofosmin). The principles of viability detection by SPECT mainly rely on demonstrating reversible stress perfusion defects in dysfunctional segments. Areas with persistent little or no tracer uptake indicate non-viable myocardium unlikely to recover function after revascularization. Stress can be performed either after physical exercise or after vasodilation with dipyridamole, adenosine, or regadenoson. Rest-only images demonstrating preserved or only mildly reduced perfusion are also indicative of myocardial viability.

Thallium has higher first pass extraction than sestamibi and tetrofosmin and, unlike ^{99m}Tc -labelled tracers, it is released by the cells allowing late redistribution imaging after a single injection. SPECT assessment of myocardial viability with thallium includes either stress-redistribution or rest-redistribution protocols.⁶⁵ Late redistribution of the tracer after a stress or rest injection is considered indicative of viable myocardium. To enhance this phenomenon, resting reinjection of a supplementary dose of tracer can also be considered. The particular pattern of 'reverse redistribution', i.e. a perfusion defect which appears worse on the delayed than on the initial images, is thought to be related to hyperaemic blood flow that causes enhanced uptake of thallium in the initial post-stress images with a more rapid clearance of the tracer and is also consistent with viable myocardium.⁶⁶

As compared with thallium, ^{99m}Tc -labelled radiotracers are generally preferred because of their shorter half-life (6 vs. 73 h), resulting

in more favourable dosimetry, and higher photon energy (140 Kev instead of 68–80 Kev), allowing better quality of ECG-gated images. SPECT assessment of myocardial viability with ^{99m}Tc -labelled tracers include stress–rest protocols, modified nitrate-enhanced rest imaging, and combined assessment of perfusion and function with gated SPECT^{67,68} (Figure 5).

For the acquisition of SPECT images, ECG gating and attenuation correction techniques are recommended.⁶⁹ Interpretation should be performed using a 17 segment AHA model including visual interpretation of uptake and reversibility of perfusion defect, summed stress, rest, and difference scores as well as semi-quantitative assessment of tracer activity and defect size. Reporting should also include measurement of LVEF and wall thickening at stress and rest.⁷⁰ A dysfunctional myocardial segment with a reversible perfusion defect indicating ischaemia, or preserved or mildly depressed resting perfusion (relative tracer uptake exceeding >50 or >60% of remote myocardium) or a positive rest-redistribution thallium scan are all considered viable.

In a meta-analysis, SPECT was reported to have a high (87%) sensitivity but relatively low (54%) specificity in predicting post-revascularization recovery.⁷¹ Advantages of SPECT are its wide availability, high standardization, and reproducibility of results. Possible disadvantages include the duration of the protocol and the radiation dose which are substantial with the use of thallium (up to 4 h and 20 mSv), but can be drastically reduced with the use of ^{99m}Tc -labelled tracers,

Key point 5:

- i. Dysfunctional myocardium with stress-induced ischaemia is considered viable.
- ii. Dysfunctional myocardium with preserved resting perfusion (>50–60% of the remote myocardium) is considered viable.
- iii. Dysfunctional myocardium with rest-redistribution of thallium is considered viable.

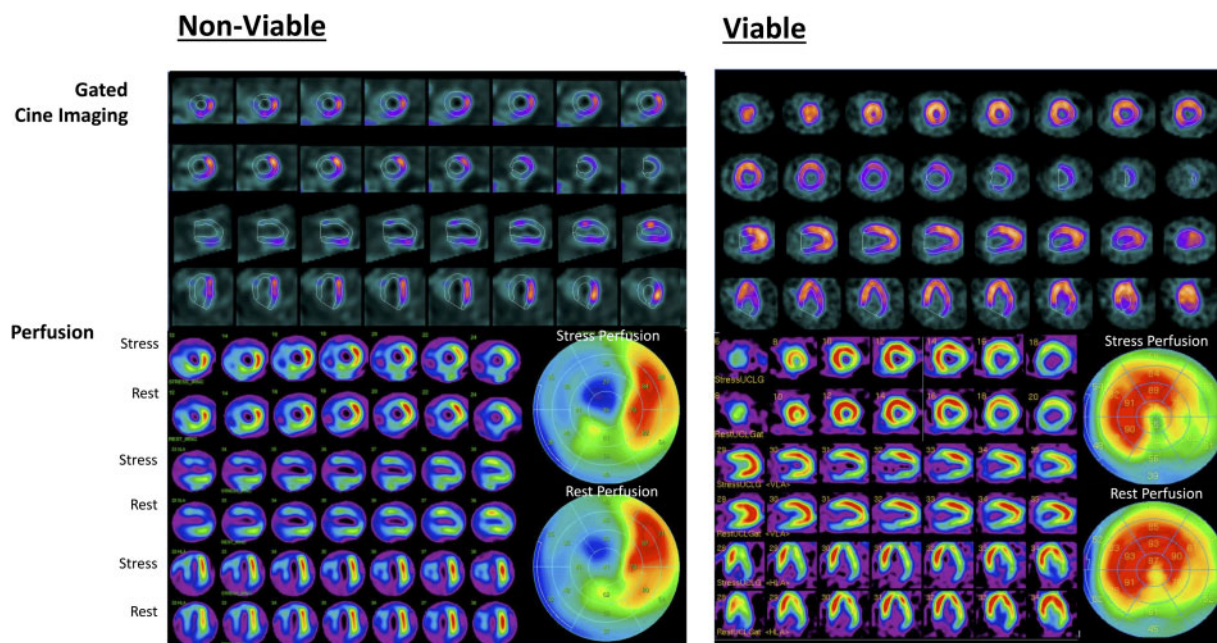


Figure 5 Detection of myocardial viability by SPECT. Example of a patient with, respectively, non-viable and viable dysfunctional myocardium. Top row shows end-systolic-gated cine images. Bottom row shows matched perfusion stress rest images and polar maps. Left panel: non-viable myocardium: images from a 76-year-old male with 3-vessel disease and occlusion of his proximal LAD. Cine images demonstrate anterior, anterior, and septal akinesia with reduced LVEF (42%). Perfusion imaging demonstrated severely reduced apical, septal anterior, and infero-basal perfusion at stress, without improvement at rest. Right panel: viable myocardium: images from a 67-year-old male with LVEF was 36% with inferior and infero-lateral akinesia. Coronary angiography demonstrated total occlusion of left circumflex and right coronary artery. Perfusion imaging demonstrated mild inferior hypoperfusion at stress with improvement and maintained inferior perfusion at rest. See also [Supplementary data](#) online, [Movie S2](#). LVEF, left ventricular ejection fraction; SPECT, single photon emission computed tomography.

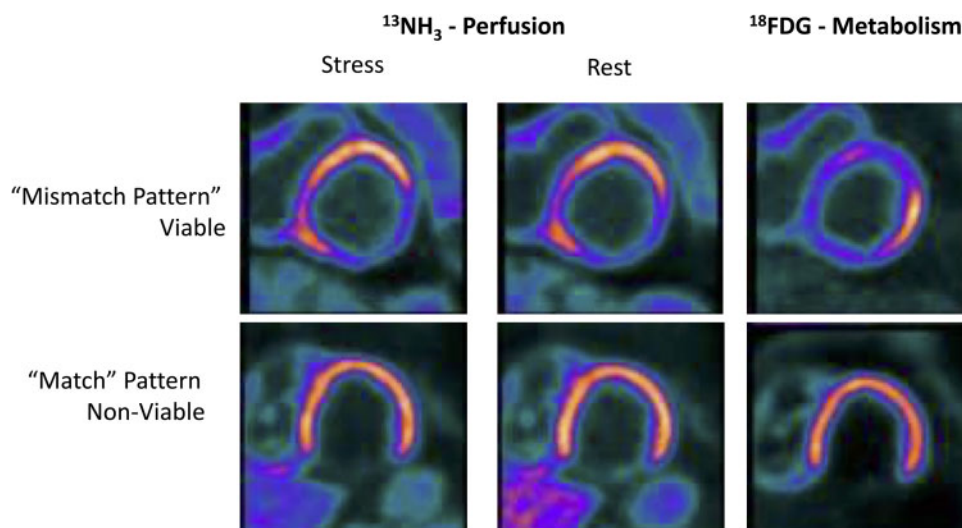


Figure 6 Detection of myocardial viability by combined NH_3 and ^{18}F -FDG PET. Viability in dysfunctional myocardium is evaluated by comparing myocardial perfusion ($^{13}\text{NH}_3$) with metabolism (^{18}F -FDG) uptake patterns. Normal NH_3 and ^{18}F -FDG or normal ^{18}F -FDG in the presence of slightly reduced perfusion (mismatch pattern) is considered indicative of viable myocardium. Severely reduced perfusion and glucose uptake (match pattern) is considered indicative of scar (non-viable myocardium).

particularly when combined with modern higher efficiency (such as CZT) cameras (1 h and 3–5 mSv). The limited spatial resolution of the technique precludes evaluation of subendocardial scars.

PET imaging of viability

PET provides direct and detailed assessments of myocardial perfusion, metabolism, and viability.^{4,72} Myocardial PET perfusion studies can be performed with the generator-produced Rubidium-82, the cyclotron-produced N-13 ammonia, O-18 water, or more recently F-18 flurpiridaz. These provide more accurate information on myocardial perfusion⁷³ than other techniques and allow absolute quantification of myocardial blood flow (MBF), improving our pathophysiological understanding of viable myocardium, facilitating the detection of balanced micro and macrovascular ischaemia, and providing strong prognostic information.^{74,75}

Uniquely PET allows direct assessment of myocardial metabolism and therefore viability in areas of dysfunctional myocardium.^{76,77} Multiple different PET tracers have been used to assess these metabolic pathways, although in the clinical setting, ^{18}F -fluorodeoxyglucose (^{18}F -FDG) is the best studied and most widely used approach. The ^{18}F -FDG is a glucose analogue that is taken up by metabolically active cells via the GLUT 1 and GLUT 4 glucose transporters. Inside the cell ^{18}F -FDG is phosphorylated by the actions of hexokinase to form ^{18}F -FDG-6-phosphate, a molecule that cannot undergo further metabolism becoming trapped within the cell and accumulating according to the activity of the GLUT transporters and hexokinase. As such ^{18}F -FDG provides a useful biomarker of cell metabolic activity and viability. In the fasting state, the normal myocardium relies mainly on fatty acid metabolism whilst, in the fed state, glucose uptake increases and accounts for virtually all energy conversion. PET

viability protocols require patient preparation to simulate the fed state and stimulate myocardial glucose utilization. These may include the administration of an oral glucose load (75 g), an insulin glucose clamp, or the oral administration of the lipid lowering agent acipimox, a niacin derivative which blocks the utilization of free fatty acids by the myocardium.⁷³ Because of the variable effects of a glucose load, particularly in patients with diabetes mellitus or glucose intolerance, the insulin glucose clamp or acipimox are preferable providing more reliable stimulation of myocardial glucose metabolism and thus better image quality. Non-invasive imaging of ischaemia and viability by ^{18}F -FDG PET relies on the observation that myocardial tracer uptake is increased by hypoxia and mild to moderate ischaemia, decreased (but still detectable) in chronic severe ischaemia and absent in scarred non-viable myocardium. Regions of myocardium that demonstrate preserved ^{18}F -FDG uptake are considered viable whilst those with absent ^{18}F -FDG uptake are deemed non-viable.

The interpretation of myocardial viability studies by PET is usually performed by combining assessments of metabolism and perfusion. Thus, the PET viability imaging protocol first includes a myocardial perfusion PET study (using ^{82}Rb -Rubidium, N-13 ammonia, or O-18 water) to assess resting perfusion, possibly combined with an additional pharmacological stress perfusion study to assess inducible ischaemia. In the same or a different session, an ^{18}F -FDG PET scan is acquired 60–90 min after tracer injection to assess metabolic activity.¹¹ Comparison is then usually made between the rest perfusion and FDG scans. The following four patterns (Figure 6) can be identified for each myocardial segment. (i) *Normal pattern with preserved perfusion and metabolism* which is observed in areas of healthy myocardium but can also be observed in stunned dysfunctional myocardium following a transient but intense ischaemic episode. (ii) *Matching*

pattern with reduced perfusion and reduced metabolism identifying non-viable segments with irreversible scar. (iii) *Mismatch pattern with reduced perfusion but preserved metabolism*, which is the cardinal feature of hibernating myocardium, where the myocardium is ischaemic but yet retains metabolic activity, viable⁶⁴ and with the potential to regain function following revascularization.^{72,78} (iv) *Reverse mismatch pattern, where myocardial metabolism is impaired despite normal perfusion*, which can occur in non-ischaemic cardiomyopathy, left bundle branch block, or diabetes mellitus and may reflect myocardial scarring due to non-ischaemic disease processes.

Key point 6:

- i. 18F-FDG uptake is dependent on preserved metabolic activity in the myocardium and should be evaluated during a glucose clamp or after apicimox administration.
- ii. PET measurements of perfusion and 18F-FDG uptake should be preferentially expressed quantitatively.
- iii. Dysfunctional myocardium with normal rest perfusion (>70% of remote myocardium) and normal 18F-FDG uptake (>70% of remote myocardium) is considered viable.
- iv. Dysfunctional myocardium with reduced rest perfusion and preserved or increased FDG uptake (mismatch pattern) is considered viable.
- v. Dysfunctional myocardium with stress-induced ischaemia is considered viable.
- vi. Dysfunctional myocardium with reduced rest perfusion and reduced FDG uptake (match pattern) is considered non-viable (scar).

Overall, the two key advantages that PET myocardial perfusion-metabolic imaging holds over SPECT perfusion imaging are a higher spatial resolution, and the ability to differentiate between dead irreversibly scarred myocardium and hibernating myocardium that may yet recover function following revascularization.⁷² Moreover, the robust attenuation correction methods employed in modern PET system offer advantages compared with SPECT, particularly when imaging obese patients and females. Disadvantages of PET include its limited availability, and the relatively high associated costs and radiation exposure: approximately 11 mSv for combined perfusion and 18F-FDG protocols.

PET viability assessments have been investigated in multiple clinical studies. These confirm that segments with preserved metabolic activity, but reduced perfusion consistently demonstrate good accuracy for the detection of hibernating myocardium that will recover function following revascularization. A systematic review of 24 published studies (756 patients) by Schinkel et al.⁷⁹ demonstrated a weighted mean sensitivity of 92% and specificity of 63% with a PPV of 74% and NPV of 87% for the prediction of recovery in regional function. This excellent sensitivity was superior to each of the other imaging modalities analysed (gated SPECT, CMR, and dobutamine stress echocardiography). Specificity was similar to SPECT imaging but was not as good as stress echocardiography. Results were similar in a health technology assessment that described a pooled sensitivity of 92% and specificity of 68% for 18F-FDG PET in predicting recovery of regional

wall motion.⁸⁰ In the PARR-1 study the extent of myocardial scarring on PET was an independent predictor of ventricular recovery following revascularization with the greatest improvement in patients with the least scar.⁸¹ The PARR-2 randomized controlled trial investigated the utility of 18F-FDG PET-assisted management in 430 patients with severe LV dysfunction and suspected coronary artery disease compared with the standard of care.⁸² PARR-2 was a neutral trial with no improvement in outcomes observed with the use of PET imaging. However, in a *post hoc* analysis patients with the most extensive degree of perfusion-metabolism mismatch did appear to gain benefit. A threshold of >7% viable myocardium appeared to identify patients most likely to benefit.⁸³ Results were similar in a subsequent observational study of 648 patients where PET was used to assess ischaemia and viability in patients with moderate to severe LV dysfunction.⁸⁴ Here a threshold of >10% identified patients that benefited from revascularization. An on-going randomized clinical trial will further test the hypothesis that 18F-FDG viability imaging improves clinical outcomes.⁸⁵

Cardiovascular magnetic resonance

CMR allows comprehensive assessment of patients with coronary artery disease. Myocardial wall thickness and regional function as well as global LV function can be assessed with high precision and accuracy in normal as well as deformed hearts and contribute to the assessment of viability. The principal method for assessing viability by CMR is detection of scar and scar extent by LGE. Dobutamine stress CMR may be complementary for improved accuracy when LGE predicts the probability of recovery to be indeterminate. Recently, T1 mapping techniques have also demonstrated promise with further confirmation studies awaited. CMR may also evaluate coronary flow reserve by stress perfusion imaging. Finally, spectroscopic techniques have been used to evaluate metabolism in viable myocardium.

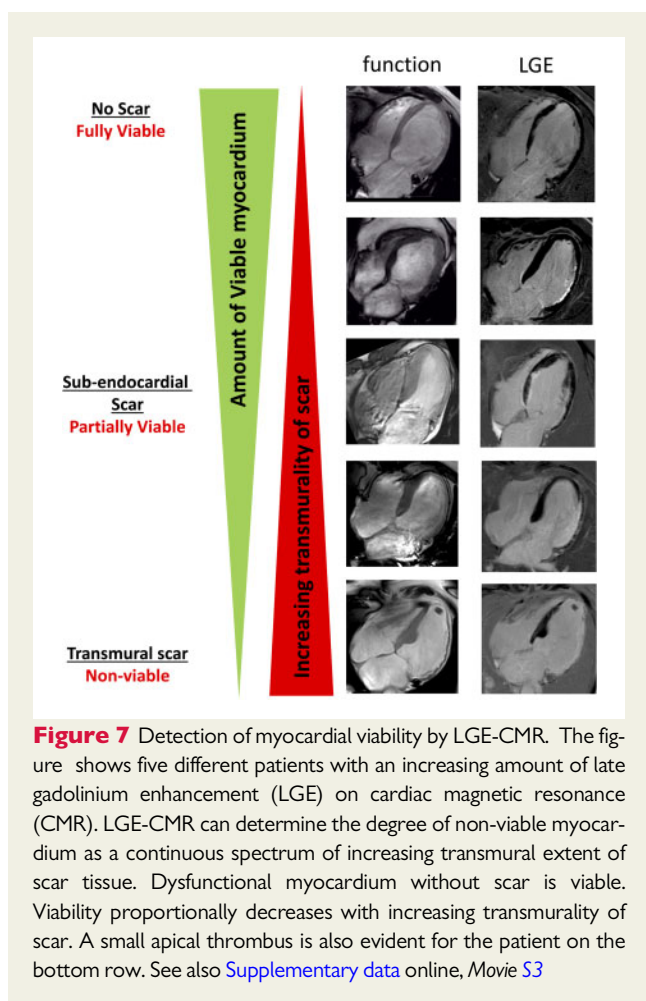
Evaluation of resting function and wall thickness

CMR cine sequences allow precise evaluation of resting wall motion and LV function. In a comprehensive protocol, the regional contractility is compared with presence of LGE for evaluation of viability in dysfunctional segments. Some studies have also used measurements of wall thickness alone to predict viability and found that extreme wall thinning (<5 mm) had high sensitivity but lacked specificity to predict non-viable myocardium, as these areas may sometimes still retain viability.⁷¹ Assessment of regional contractile function may be enhanced further by regional strain data computed from tagged images or by feature-tracking analysis.

Late-gadolinium enhancement

LGE has become the reference standard for the non-invasive imaging of myocardial scar and focal fibrosis in both ischaemic heart disease and non-ischaemic cardiomyopathy.

Clinically used gadolinium-based contrast agents are distributed into the extracellular space following intra-venous injection. They are therefore present in higher concentration in fibrotic or infarcted myocardium. This is best observed 10–15 min after contrast injection, when difference to normal myocardium are maximized, using the



'LGE' technique. LGE-CMR sequences are timed to selectively null signal in normal myocardium, which appears black, whereas areas of scarring with shorter T1 values appear bright. LGE affords high contrast to noise ratio as well as its excellent spatial resolution (approximately 1×1 mm in-plane) allowing the visualization of scar with near histological precision. The latter allows precise estimation of infarct size⁸⁶ and in particular the transmural extent of scarring. This technique has been extensively validated against histopathology. *LGE-CMR therefore images non-viable myocardium and infers viability from the absence of enhancement.*

LGE imaging protocols have been standardized. Inversion recovery sequences, preferentially with phase-sensitive inversion recovery pulses should be used with images acquired in different directions (stack of contiguous short-axis and 2, 3, and 4 chamber long axis views). Interpretation of LGE images can be performed visually, but ideally should be performed quantitatively.^{87,88}

The transmural extent of LGE ([Figure 7](#)) is inversely related to the likelihood of improvement of regional LV function following revascularization.⁸⁹ In chronic CAD, segments with less than 25% transmural hyper-enhancement of LGE have high probability of functional recovery while hyper-enhancement >75% of the wall thickness are very

unlikely to recover function early and up to 6 months.⁹⁰ Similar predictive values of LGE extent were reported in acute MI.⁹¹ However, the predictive accuracy of LGE is limited in segments with transmural extent between 25% and 75%, which display an intermediate likelihood of functional recovery. This was shown in a meta-analysis of 11 studies where LGE had 91% sensitivity but only 51% specificity for predicting recovery of regional function.⁹² LGE assessment has been found useful in cases of regional wall thinning, for predicting functional recovery after revascularization.⁹² Shah et al.⁹³ showed that in thinned segments (wall thickness ≤ 5.5 mm) but transmural scar extent of $\leq 50\%$ recovery of function and restoration of normal wall thickness after revascularization are likely. Of note, the presence of viable myocardium as detected by LGE may not translate directly to functional recovery when there is insufficient amount of viable residual myocytes to ensure functional recovery, in the presence of advanced forms of LV remodelling, and due to the variability in the success of revascularization. Functional recovery analysis using may be improved by using strain imaging in addition to qualitative visual assessments.⁹⁴

The relationship between LGE viability and global recovery of LV dysfunction, as assessed using ejection fraction, has been examined by several studies as well. The presence of 10 or more viable segments in patients with wall motion abnormalities before revascularization, predicted $\geq 3\%$ improvement in LVEF, with a sensitivity of 95% and a specificity of 75% for positive remodelling.⁹⁵ The absolute thickness of viable tissue also predicts functional recovery with overall wall thickness proving less accurate.⁹³ LGE volume and transmural extent are independent predictors of mortality, with incremental value to LVEF and LV volumes.⁹⁴ In different studies, LGE volume was the strongest predictor of late LV dysfunction with a HR of 6.1 for adverse events for an LGE extent $\geq 23\%$ ⁹⁶ and predicted LV reverse remodelling after cardiac resynchronization therapy.⁹⁷ Finally, the quantification of the peri-infarct grey zone around dense scar, which depicts a mix of viable myocytes and collagen fibres and provides re-entry circuits for ventricular arrhythmias, was found to be a strong predictor of appropriate ICD discharges in patients with ischaemic cardiomyopathy.⁹⁸ Also retrospective studies using LGE for detecting viability, have suggested that the HR of death in patients with viable myocardium as detected by LGE treated medically is higher in comparison with those who were completely revascularized.^{99,100}

The principal advantages of CMR LGE are the high quality of images, absence of ionizing radiation, high prognostic value, and lower costs relative to nuclear imaging. Disadvantages include the need for gadolinium-based contrast injection, which although generally safer than iodinated contrast agents, can cause allergic reactions and anaphylaxis. Also, gadolinium-based contrast agents are considered contraindicated in pregnancy, although a recent study showed that in the second and third trimesters, CMR can be safely performed even with contrast.¹⁰¹ Finally, LGE shows the expansion of the extracellular matrix, regardless of whether this is due to collagen, water, or amyloid infiltration. As a result, LGE may overestimate the extent of the scar if there is myocardial oedema, in particular in acute myocardial infarction.

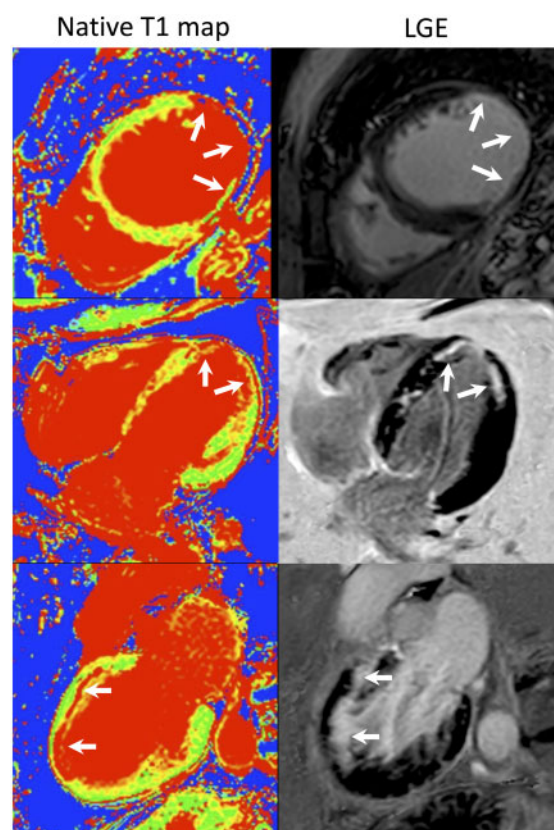


Figure 8 Cardiovascular magnetic resonance (CMR) myocardial characterization of myocardial viability through quantitative measurement of native (non-contrast enhanced) T1 times in comparison with LGE. Characterization of myocardial viability by quantitative measurement of native (noncontrast) T1 in comparison with late-gadolinium enhancement (LGE) on CMR. Non-viable scar tissue has increased native T1 time. In these examples, regions of high T1 correspond to areas of late hyperenhancement (LGE). However, it should be noted that native T1 is non-specific for scar, as it may also increase due to other conditions, such as amyloid infiltration, and oedema.

Dobutamine stress CMR

Like stress echocardiography, the evaluation of contractile reserve using dobutamine stress CMR can be used to assess viability. Steady-state free precession (SSFP) cine sequences generate excellent blood pool-myocardial definition which can be exploited for the assessment of wall thickening in response to inotropic stress. Infusion of low-dose dobutamine (5–10 $\mu\text{g/kg/min}$) induces systolic wall thickening in viable regions of myocardium but not in irreversibly scarred areas. If this contractile reserve can be elicited, the myocardium is more likely to improve after revascularization. In addition, low-dose dobutamine can accurately predict the development of adverse remodelling following acute myocardial infarction.¹⁰² With high-dose dobutamine infusion (20–40 $\mu\text{g/kg/min}$), the presence of inducible wall motion abnormalities using cine CMR can trigger a biphasic response and provides additional accurate information regarding the presence of ischaemia and prognosis.¹⁰³

The use of dobutamine stress CMR predates vasodilator stress perfusion.¹⁰⁴ Using FDG-PET as the gold-standard, inotropic response to dobutamine in combination with wall thickness measurements predicts viability with a high sensitivity, specificity, and positive predictive accuracy (88%, 87%, and 92%, respectively).¹⁰⁵ With functional recovery following revascularization as the gold-standard, dobutamine CMR also performs well. In addition, the absence of functional recovery is predicted in areas graded as scar which do not exhibit contractile reserve with a negative predictive accuracy of at least 85%.¹⁰⁶ Predicting global recovery of myocardial function is however more robust than the prediction of recovery of regional myocardial contractility on a per-segment basis.¹⁰⁷ Although most trials have involved small numbers, a meta-analysis of 331 patients using low-dose dobutamine CMR, and a cut-off of 50% transmural LGE hyper-enhancement reported a sensitivity of 95% and specificity of 51% for predicting functional recovery.⁹²

Results suggest that low-dose dobutamine CMR is superior to both LGE CMR and wall thickness (using a cut-off value of 4 mm) in predicting recovery after revascularization.^{108,109} This is particularly relevant for detecting viability in patients with intermediate grades of transmural infarction (up to 75% extent of LGE), but its sensitivity may be reduced with more severely impaired baseline LV function and those patients with fewer than 50% of all myocardial segments deemed viable may derive less benefit from revascularization.^{109,110} Interestingly, there is a strong correlation between LV ejection fraction (LVEF) measured during low-dose dobutamine (10 $\mu\text{g/kg/min}$) and LVEF 6 months after revascularization.¹⁰⁹

The combined use of LGE and low-dose dobutamine stress CMR, has a higher specificity (91%) and a lower sensitivity (81%) according to a meta-analysis,⁹² and is expected to lead to an increased accuracy for predicting regional function recovery compared with individual methods.

The inotropic response to dobutamine is strongly associated with abnormalities of fatty acid metabolism and is likely to depend on the presence of viable myocardium which has not undergone severe ultrastructural change with myofibrillar degeneration which would otherwise prevent contractile improvement with inotropic stimulation.^{108,111} The combination of dobutamine stress with other CMR sequences can give a more accurate assessment of both ischaemia and viability, with the potential to improve diagnostic performance.^{92,112,113}

Non-contrast imaging techniques

Recently new parametric sequences have been developed to allow measurement of native myocardial T1 and T2 magnetization recovery times as well as computation of extracellular volume (ECV) on a voxel by voxel basis.^{114,115} The principal interest of these methods is that these parameters may provide refined information on diffuse disease affecting both myocardial cells and the interstitium.¹¹⁶ Native T1 times are higher in fibrotic tissue than myocardium and thus non-viable myocardium could potentially be detected by increased T1 time.^{117,118} However, changes in T1 times alone are relatively non-specific, as they can also be altered by other structural changes in myocytes and/or the extracellular matrix, including the presence of oedema, amyloid, iron, or fat. In some cases, a combination of two processes can lead to pseudo-normalized or even decreased native T1. T2 relaxation times of the tissue mainly depend on water

Key point 7:

- i. CMR LGE is currently the reference method for clinical assessment of viability and indicates myocardial necrosis or chronic scar.
- ii. Delay after contrast injection and timing of inversion recovery pulses are crucial for image quality.
- iii. Scars with transmural >50% are considered non-viable, less transmural scar in dysfunctional myocardium is considered viable myocardium.
- iv. LGE has high specificity for predicting absence of recovery but sensitivity may be limited particularly in scars with intermediate transmural (25–75%).
- v. Low-dose dobutamine stress MR may have additional value in such patients with intermediate transmural scar.
- vi. Stress perfusion CMR also allows evaluation of ischaemia and coronary flow reserve.
- vii. New post-contrast T1 and ECV mapping techniques allow refined detection of myocardial disease and may supersede LGE in the future.
- viii. Spectroscopy allows assessment of Na content and phosphorus metabolism, however only in experimental setting.

content^{119,120} and allows detection of myocardial oedema, and in particular assessment of the myocardial area at risk when measured between 2 and 7 days after acute MI. However, detection of myocardial oedema alone is not specific for non-viable tissue, as viable myocardium may in the acute phase also be oedematous.

Combined T1 mapping pre- and post-contrast, allows estimation of the ECV, fraction of the myocardium. In the absence of amyloid or oedema, ECV measurements represent interstitial or focal fibrosis as markers of myocardial remodelling. As compared with native T1, ECV is more accurate and reproducible, less dependent on external factors, easier to compare between different scanners, and has better agreement with histological measures of fibrosis. So far, however, mapping techniques have mainly been used in acute myocardial infarction where the combination of T1 T2, and ECV/LGE can depict the main pathophysiological process that occur following acute MI, i.e. the detection of oedema, microvascular obstruction, and intra-myocardial haemorrhage.¹²¹ There is currently less data for T1 mapping and ECV in the assessment of viability in chronic MI, as in chronic MI replacement fibrosis and scar will exhibit less substantial increases in native T1 values than are observed in the acute stage. A potential advantage of native T1 mapping is that the injection of contrast media can be avoided (Figure 8). This indication would be of high practical interest in patients in whom administration of GCA is contraindicated. Both native T1 and ECV have also been used to evaluate chronic MI transmural in several small studies^{122–125} showing potential for identifying non-viable myocardium and infarct size. Unfortunately, variability in native T1 and its dependency on external factors such as magnetic field,¹²⁶ scanner manufacturer and model, type of pulse sequence etc.^{127,128} makes it difficult to set cut-off values to define regions of acute or chronic MI. However, ECV values are markedly elevated in chronic MI, up to doubled compared

with normal myocardium, but slightly lower than in acutely infarcted myocardium ($53 \pm 10\%$).¹²⁹ The extent of focal areas of increased ECV on maps correlates strongly with LGE and provides comparable information as LGE but in a more quantitative manner. Therefore, ECV maps are likely to replace LGE for viability assessment in the future.

Key point 8:

- i. Principal use of CT is defining the presence and severity of coronary artery disease.
- ii. CT-delayed imaging may detect late-enhancement similar to LGE-CMR.
- iii. Limitations are inferior image quality than CMR for late-enhancement, radiation exposure, and increased contrast volume.
- iv. At present CT late-enhancement remains predominantly a research tool.

New sequences that acquire simultaneous T1 and T2 mapping will likely make quantitative CMR imaging efficient and therefore suitable for clinical practice.¹³⁰

Finally, CMR spectroscopic techniques have been employed in experimental setting to evaluate myocardial ²³Na concentration as marker of membrane function and myocardial ³¹P-Creatinine/ATP ratio to evaluate myocardial energy homeostasis.

Computed tomography

The principal value of computed tomography (CT) is precise evaluation of the underlying coronary anatomy. This can be combined with information from nuclear imaging obtained on hybrid SPECT-CT or PET-CT scanners, allowing more accurate superposition of tissue viability with coronary anatomy assessments. CT coronary angiography may however also directly detect areas of myocardial infarction via the identification of left ventricular wall thinning and regional wall motion abnormalities with retrospective gating protocols. Moreover, CT can detect myocardial scarring and fibrosis directly using the presence of persistent contrast on delayed imaging, which was first described in 1976, earlier than MR.¹³¹ Indeed, similar to the principles of LGE on MR, iodinated CT contrast agents have higher distribution volume and wash out of regions of replacement myocardial fibrosis or scarring more slowly than out of areas of normal healthy myocardium. Increased signal/attenuation is therefore observed in these areas if imaging is performed at delayed time points, informing about both the presence and pattern of myocardial scarring in the left ventricle. In contemporary studies, CT late enhancement has demonstrated moderate diagnostic accuracy in the detection of MI (sensitivity 52–78%, specificity 88–100%),¹³² with several techniques (e.g. low-tube voltage, dual energy imaging, and increased contrast volume) being explored to improve scar visualization.¹³³ Image quality of CT-late enhancement however remains inferior to CMR and the radiation dose is between 1 and 5 mSv. CT-based estimation of ECV are also possible, again using a similar approach to CMR.^{134,135} These

Table 2 Strengths and weaknesses of different imaging methods for detection of viability

	LDD-TTE	SPECT	PET	CMR
Advantages/disadvantages				
Availability	Widespread	Widespread	Limited	Variable
Cost	Low	Moderate	High	Moderate
Operator dependency	High	Low	Low	Low
Radiation exposure (mSv)	0	²⁰¹ Tl: 3–10 mSv ⁹⁹ Tc: 20 mSv	¹³ NH ₃ : ±4 mSv ¹⁸ FDG: 5–7 mSv	0
Spatial resolution for detection of viable myocardium	Transmurality	10–15 mm	4–5 mm	1–2 mm
Duration of exam	45 min	2 × 25 min	2 h	30 min
Contraindications	Poor acoustic window Acute coronary syndrome Hypertrophic obstructive cardiomyopathy Uncontrolled hypertension Uncontrolled heart failure Severe ventricular arrhythmias	Pregnancy	Pregnancy	(Pregnancy) Claustrophobia Non-MR compatible devices (advanced renal failure)

CMR, cardiovascular magnetic resonance; LDD, low-dose dobutamine; MR, magnetic resonance; PET, positron emission tomography; SPECT, single photon emission computed tomography; ¹⁸F-FDG, ¹⁸F-fluorodeoxyglucose.

potentially provide assessment of both replacement and diffuse interstitial fibrosis, with further validation studies required in patients with ischaemic cardiomyopathy. Therefore, at present CMR fibrosis assessments are generally preferred and CT is still primarily considered a research tool to be used clinically in expert centres when other imaging modalities are contra-indicated.¹³⁶

Comparison of techniques

Echocardiography, tomographic nuclear imaging (SPECT and PET), and CMR are available clinically for viability assessment and to identify markers of functional recovery. Each of these techniques has advantages and disadvantages (Table 2). Since the tests evaluate different aspects of myocardial viability, and may use different cut-off values to identify viable myocardium, in clinical practice, clinicians may be confronted by discordant results in individual patients. This is illustrated by examples in Figures 9–11.

Comparison of diagnostic accuracy for the different myocardial viability is problematic in the absence of a clinically available gold standard. Hard clinical outcomes, such as all-cause mortality, or improvement in regional or global left ventricular function following revascularization, are therefore important methods for assessing the utility of viability assessments but are themselves multifactorial and influenced by multiple other factors (for example, the completeness and success of revascularization in ischaemic cardiomyopathy). Another point of concern is that the definitions of viability and clinical outcomes have varied across different studies with different cut-offs frequently applied for the same imaging techniques. Finally, the current literature is limited regarding head-to-head comparisons of the

different viability techniques. The available data from two meta-analyses are reported in Table 3.

An early review of the topic in 2004 mainly listed nuclear techniques, along with dobutamine stress echo. Summarizing results from 18 head-to-head studies comparing nuclear with stress echo, the review concluded '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%).'¹⁷¹ Since that review, with implementation of the concept of scar thickness as a predictor of functional recovery, CMR has become the dominant clinical modality for the diagnosis of myocardial viability in Europe,¹³⁷ despite debatable diagnostic accuracy in the intermediate range of infarct transmural thickness.

In the first major comparative study, Klein *et al.*¹³⁸ performed contrast CMR and PET for metabolism and perfusion in 31 patients with ischaemic cardiomyopathy, finding high agreement between zones of CMR contrast enhancement and PET perfusion/metabolism mismatch.

Another small early study comparing FDG-PET with CMR¹³⁹ found that a viable rim > 4.5 mm thickness on contrast-enhanced CMR or >50% FDG uptake (compared with the segment of highest uptake) predicted recovery of regional function (measured quantitatively by CMR with a centreline method as improvement in thickening ≥ 15%) a year after revascularization (*n* = 10). Lack of viability signs predicted absence of functional recovery. The two parameters of viability correlated relatively well.

A further study¹⁴⁰ compared contrast CMR with a combination of technetium SPECT for perfusion and FDG-PET for metabolism in 29 patients with ischaemic cardiomyopathy before and after

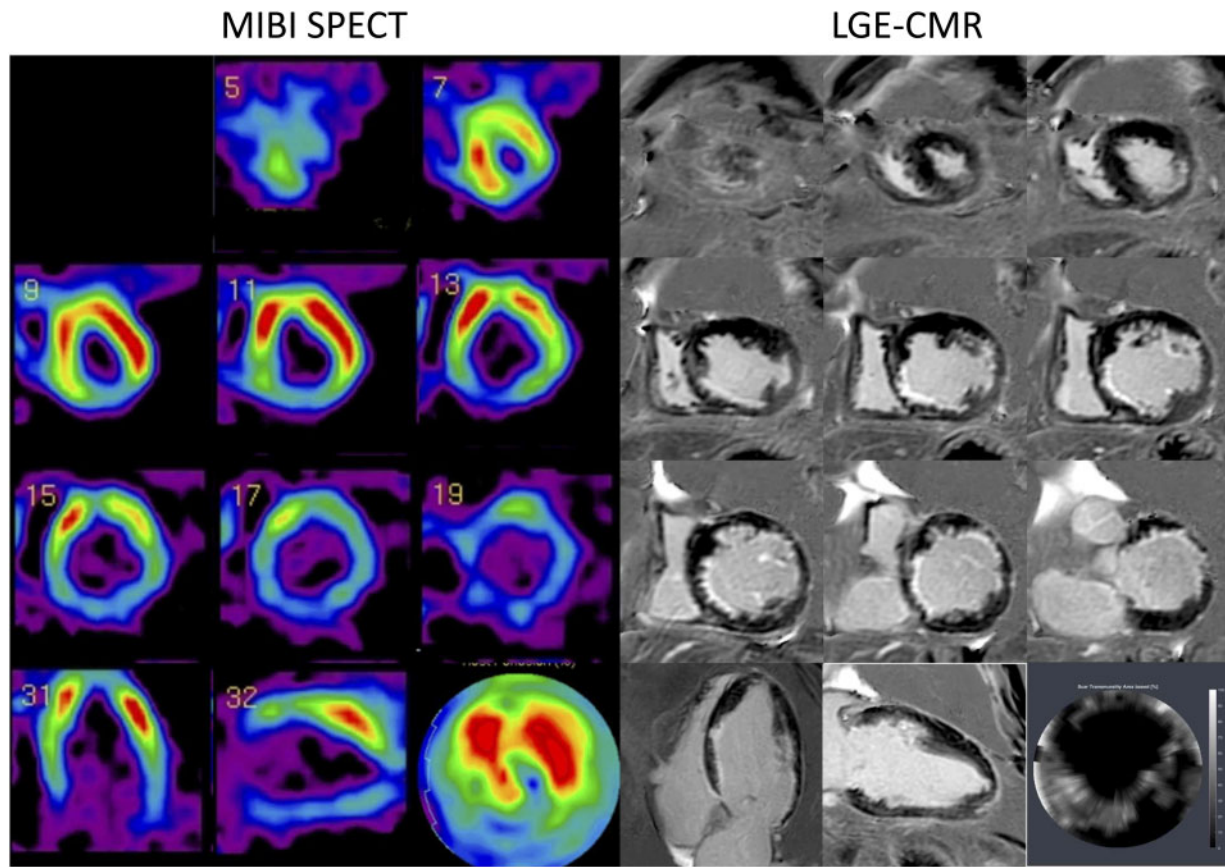


Figure 9 Example of discordant findings between SPECT and CMR. A 77-year-old patient with three vessel coronary artery disease and inferior and lateral akinesia with severe LV dysfunction (EF 36%) underwent both resting MIBI SPECT and LGE-CMR for assessment of myocardial viability. Resting MIBI SPECT shows severe hypoperfusion in septal, inferior and infero-lateral segments, suggesting absence of viable myocardium. LGE-CMR by contrast shows only small areas of subendocardial scar with <25% transmural extent, indicating relatively large amounts of dysfunctional myocardium with preserved viability. CMR, cardiovascular magnetic resonance; LGE, late-gadolinium enhancement; LV, left ventricular; SPECT, single photon emission computed tomography.

Key point 9:

- i. There is no clinical gold standard for viability imaging.
- ii. Viability testing of different pathophysiological principles related to viability may provide different results.
- iii. In direct comparison stress echo and stress CMR have higher specificity for predicting improvement after revascularization whereas SPECT, PET, and LGE-CMR have higher sensitivity.
- iv. There is no definite cut-off value for defining viability at the segment or patient levels with different cut-off-values often proposed.

revascularization. Sensitivity and specificity for the prediction of functional recovery at follow-up were 97 and 68% for CMR and 87 and 76% for PET/SPECT, with a very high negative predictive value for CMR.

Echocardiographic regional longitudinal strain was compared in a cross-sectional study of 90 patients with ischaemic cardiomyopathy with wall thickening and contrast enhancement by CMR. A cut-off for regional longitudinal strain of 4.5% differentiated between fully transmural and partially transmural scar on CMR with a sensitivity of 81% and a specificity of 82%.¹⁴¹ In another small study comparing visual scoring of resting echo, echocardiographic regional strain, and CMR-based infarct transmural, regional strain and CMR-based infarct transmural had similar diagnostic accuracy to detect and differentiate transmural from non-transmural scar, and both modalities stratified survival prognosis similarly. Visual scoring of echo was inferior to strain or CMR in distinguishing total transmural from partial transmural infarction.¹⁴²

In summary, CMR, both by infarct transmural imaging and by low-dose dobutamine wall thickening, has shown the highest sensitivity, but lower specificity, than other methods for the detection of viable myocardium. Nuclear imaging with PET has traditionally

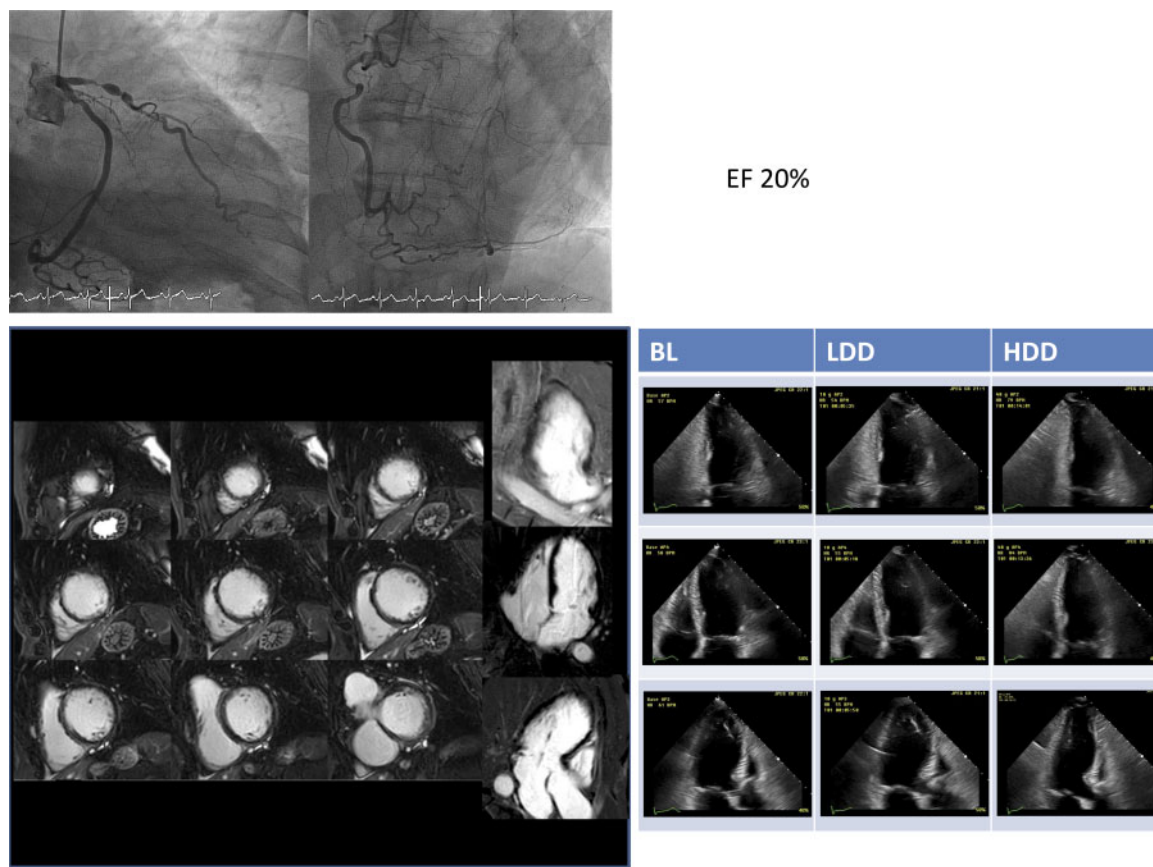


Figure 10 Example of discordant finding between dobutamine stress imaging and CMR viability. A 77-year-old male patient with 2 vessel disease (occluded LAD and first marginal branch) and anterior akinesia with severe LV dysfunction (LVEF 20%) underwent both low-dose dobutamine echocardiography and LGE-CMR. Dobutamine stress echo showed no improvement of dysfunction in apical anterior and anteroseptal segments, suggesting absence of viable myocardium. By contrast LGE-CMR demonstrates absence of scar, indicating preserved myocardial viability in all myocardial segments. See also [Supplementary data](#) online, [Movie S4](#). BL, baseline; CMR, cardiovascular magnetic resonance; HDD, high-dose dobutamine; LDD, low-dose dobutamine; LVEF, left ventricular ejection fraction; LGE, late-gadolinium enhancement.

been viewed as the best imaging method, but data showing fundamental superiority in terms of outcomes over the other methods are lacking; PET also remains unavailable in many regions. SPECT imaging has long been the workhorse of viability studies, but suffers from relatively low diagnostic specificity. Stress echocardiography requires good image quality and may increase in accuracy when including analysis of regional strain, but data are very limited for the latter. Therefore, selection of a test for viability assessment should be based on advantages, disadvantages, local experience, and availability and individual patient characteristics ([Table 2](#)). Circumstances arguing against echocardiography would be impaired image quality (e.g. in obese or emphysematous patients), against SPECT/PET the radiation exposure limiting its sequential use, and against CMR (apart from contraindications such as severe claustrophobia) an irregular heart rhythm and the need for a contrast agent in renal failure patients. Prospective head-to-head comparisons of techniques, in large populations and against clinical outcomes and functional recovery post-revascularization are lacking and desirable.

Effect of myocardial viability testing on clinical outcomes for patients

Revascularization of dysfunctional but viable myocardium may allow improvement of regional and global cardiac systolic function. Most studies evaluating the benefits of revascularizing viable myocardium have used imaging endpoints, such as ejection fraction, and demonstrated that revascularization of viable dysfunctional myocardium may improve LV dysfunction.⁷¹ Such improvements in cardiac dysfunction have been demonstrated in multiple single centre non-randomized studies^{71,92} and have subsequently been confirmed in 10 year follow-up of the randomized multicentre STICH trial.¹⁴³

Besides improving function, revascularization of viable myocardium may also have other beneficial effects such as improvement in left ventricular volumes and LV reverse remodelling, as well as improvement in patients' functional status, and heart failure symptoms. However, these surrogate endpoints have been only rarely and incompletely evaluated in most studies. A final important endpoint is improvement of survival. While revascularization of dysfunctional myocardium improves long-term survival irrespective of the presence of

myocardial viability,¹⁴⁴ surgical risk increases with the severity of LV dysfunction and dilatation. Therefore, the benefits of revascularization should be balanced against surgical risks, with viability assessments potentially useful in such decision making.

Several nonrandomized studies suggested that revascularization guided by viability assessments might improve patient outcomes.^{99,100,145} Indeed a meta-analysis of early retrospective non-randomized studies^{41,146–148} suggested benefit of revascularizing dysfunctional but viable myocardium with respect to both short- and long-term outcomes. However, these results have not been confirmed in three prospective randomized trials:¹⁴⁹ the PET And Recovery following Revascularization (PARR-2) trial,⁸² the Heart Failure Revascularization (HEART) Trial,¹⁵⁰ and most importantly the Surgical Treatment for Ischaemic Heart Failure (STICH) trial.^{143,151} In light of these randomized controlled trial data current guidelines¹⁵²

do not advocate (Class IIb indication) routine testing of myocardial viability to select revascularization of patients with heart failure.

However, considerable debate remains how these results should be interpreted,² and viability assessments remain widely used in clinical practice. Patients in STICH were not randomized to a revascularization strategy based upon their viability status. Revascularization with coronary artery bypass grafting can improve clinical outcomes by preventing future myocardial infarction as well as reversing cardiac dysfunction. Moreover, there were important potential methodological limitations of these trials.² In particular selection bias, whereby patients with LV dysfunction and clear viability may not have been randomized into the trial (hence its slow recruitment). Another major limitation of the STICH trial was that the current gold standards for assessing myocardial viability, 18F-FDG PET and LGE CMR, were not investigated. Instead STICH used SPECT and dobutamine echocardiography, two different viability assessments which provide variable results, and have different diagnostic accuracies in such populations. A major limitation of STICH, and indeed most other studies, have been that myocardial viability was considered as a binary phenomenon, rather than a continuum. This is problematic, particularly as it remains unclear what cut-off value in terms of the magnitude of myocardial viability is needed to obtain clinical benefit. Notably, the definitions of viability have varied considerably across the larger trials.² In STICH¹⁵³ ≥ 5 segments with contractile reserve on dobutamine echocardiography were considered consistent with viability, whereas ≥ 11 segments with preserved tracer uptake were required for SPECT. By contrast, the PARR-2 trial adopted a completely different approach computing the percentage scar by FDG and classifying patients as having a small ($\leq 16\%$), medium ($16\%–27\%$), or large ($\geq 27\%$) burden of scar. Reconciling these differences will be important in future trials, but challenging particularly, as the thresholds in viability that determine benefit from revascularization are likely to vary for the different modalities.¹⁵⁴ Moreover, the number of viable segments should also probably be considered in the context of the burden of irreversibly dysfunctional myocardium. Methods that can only quantify viable myocardium,

Key point 10:

Benefits of Revascularization of viable dysfunctional myocardium in coronary artery disease

- i. Improvement in myocardial function (EF/WMS) has been demonstrated after revascularization of viable myocardium in non-randomized studies.
- ii. However, there are no definite cut-off values on the number of dysfunctional viable segments, to obtain clinical benefit, as these may vary between methods.
- iii. Improved survival with viability-guided revascularization strategies has not been demonstrated in randomized trials. However, interpretation of these results is difficult due to important limitations in design.
- iv. Improvement of hospitalization rates and improvement of heart-failure symptoms and quality of life could be useful endpoint in trials assessing viability assessments but were not studied in the randomized trials.

Table 3 Criteria and diagnostic accuracy of tests for predicting segmental recovery of dysfunction after revascularization

Method (ref)	Criteria	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	PPV (95% CI)	NPV (95% CI)
LDD-TTE ⁷¹	Improvement of WMS > 1	81 (80–82)	80 (79–81)	24.53 (24.32–24.74)	77 (76–78)	85 (84–86)
SPECT						
201-Tl ⁷¹	Preserved resting perfusion or redistribution	86 (84–88)	59 (56–62)	8.79 (8.60–8.98)	69 (67–71)	80 (77–83)
99Tc tracers ⁷¹	Preserved resting perfusion	81 (78–84)	66 (63–69)	5.40 (8.60–8.98)	71 (68–74)	77 (74–80)
FDG PET ⁷¹	Preserved FDG in sector with reduced perfusion	93 (91–95)	58 (54–62)	18.16 (17.85–18.46)	71 (68–74)	86 (83–89)
CMR						
LGE ⁹²	<25% transmural	95 (93–97)	51 (40–62)	21.12 (10.98–40.55)	69 (56–80)	90 (85–93)
LDD ⁹²	Improvement of WMS > 1	81 (73–86)	91 (84–95)	41.57 (18.25–94.68)	93 (87–97)	75 (65–83)

CMR, cardiovascular magnetic resonance; FDG, fluorodeoxyglucose; LDD, low-dose dobutamine; LGE, late-gadolinium enhancement; PET, positron emission tomography; SPECT, single photon emission computed tomography.

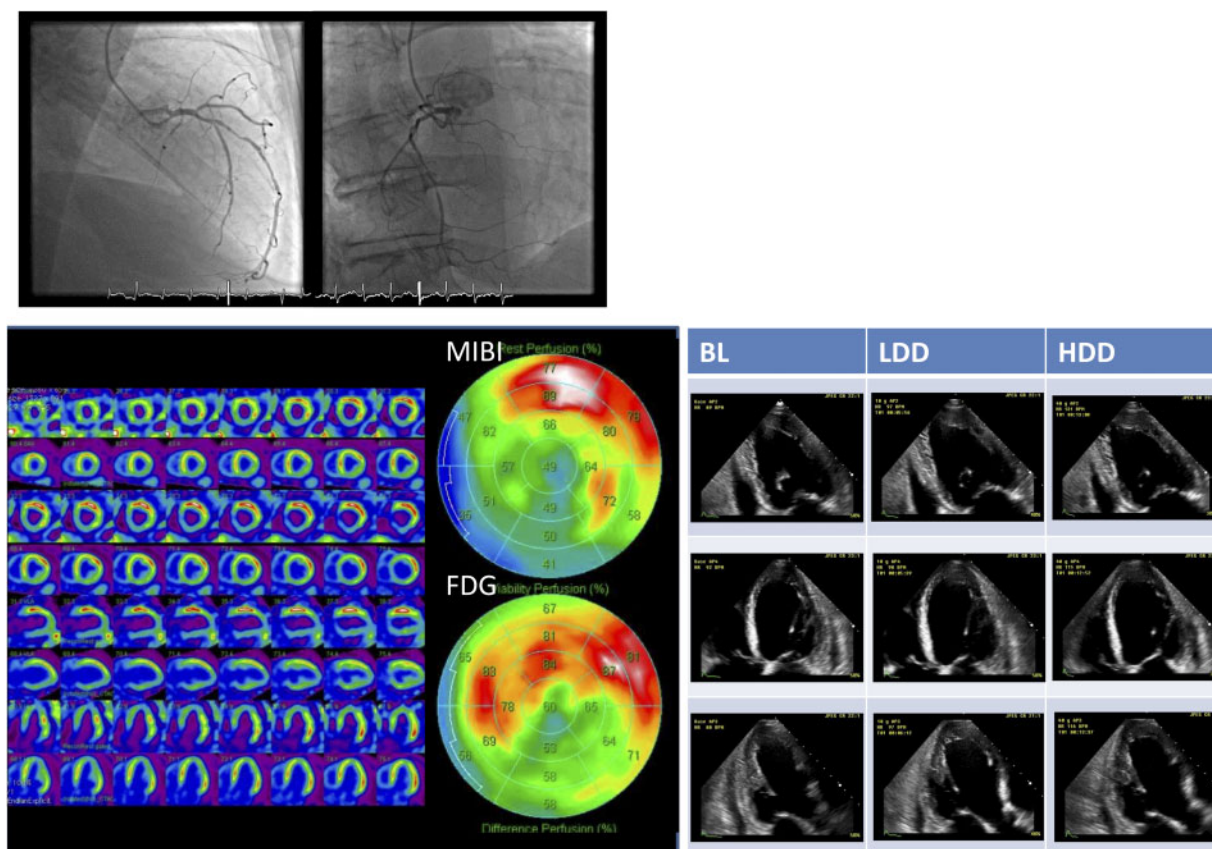


Figure 11 Example of discordant finding between dobutamine stress echo and PET. A 71-year-old male patient with three vessel and leftmain disease, severe LV dysfunction and inferior, septal and lateral akinesia underwent both low-dose dobutamine echocardiography and 18F-FDG PET for assessment of myocardial viability. Dobutamine stress echo showed no improvement of dysfunction in apical, septal, inferior, and anterior regions, suggesting absence of viable myocardium. Combined MIBI-SPECT and FDG PET by contrast demonstrated mismatch pattern in septal and lateral region, indicative of preserved viability in these regions. Only the inferior and apical regions showed matched pattern with an extent of 6% of total LV myocardium. See also [Supplementary data](#) online, *Movie S5*. LV, left ventricular; PET, positron emission tomography; SPECT, single photon emission computed tomography; 18F-FDG, ¹⁸F-fluorodeoxyglucose.

Table 4 Clinical indications for assessing myocardial viability

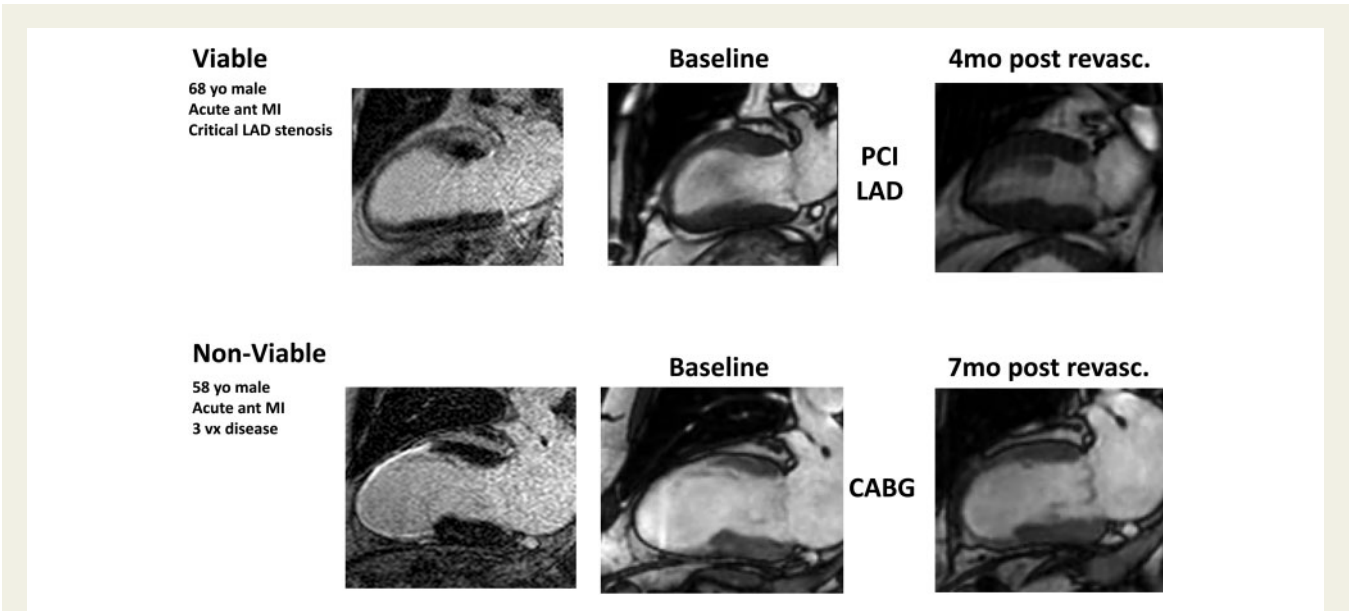
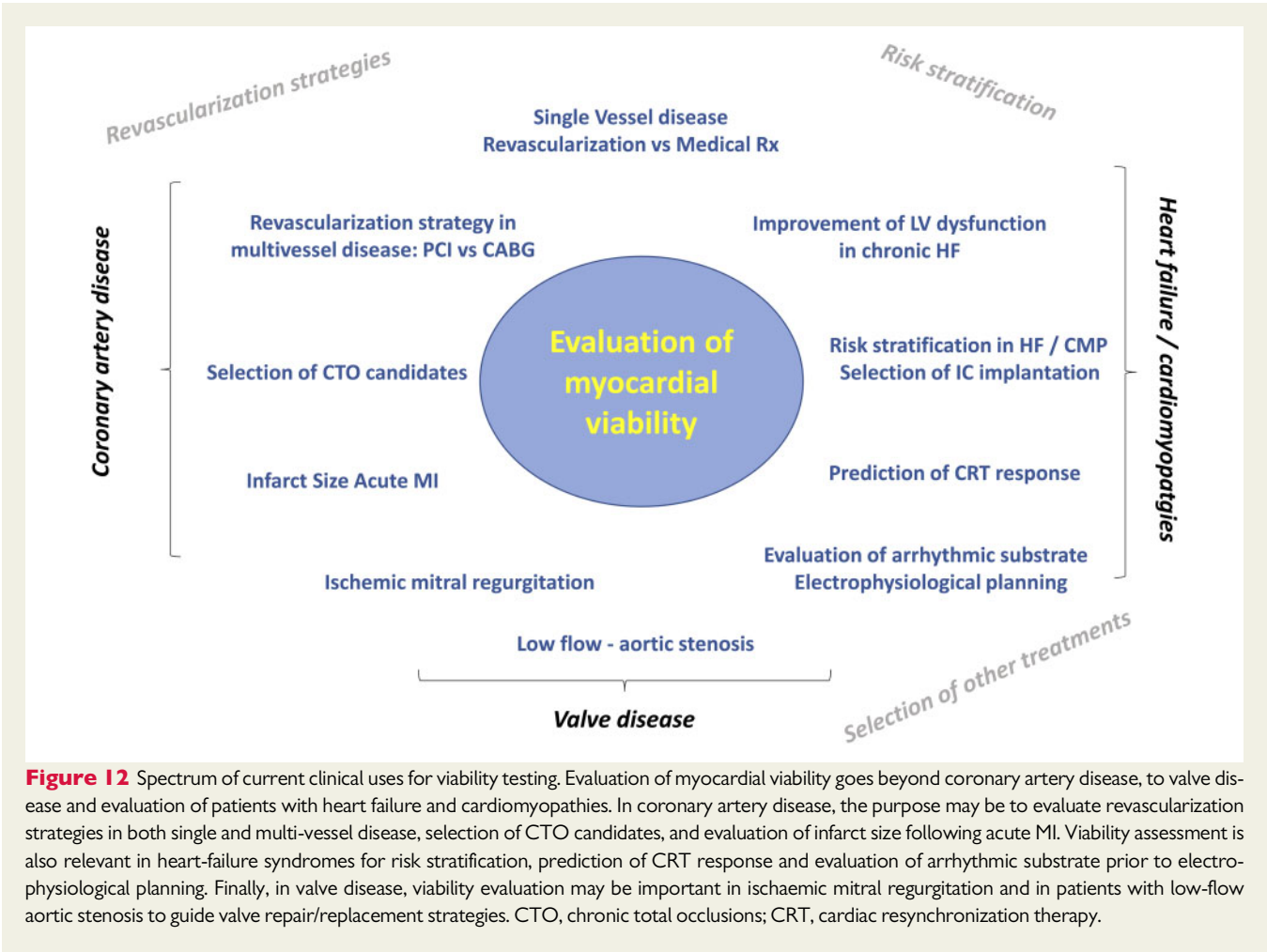
Identification of candidates for revascularization
Acute coronary syndromes with late presentation
Selection of revascularization strategies in chronic CAD
Evaluation before CTO
Chronic CAD and HF
Ischaemic mitral regurgitation
Low-flow aortic stenosis
Identification of aetiology of HF
Selection of CRT responders
EP planning of VT ablation
Identification of high-risk patients

CTO, chronic total occlusions; CRT, cardiac resynchronization therapy; FDG, fluorodeoxyglucose.

even if technically flawless (infinite spatial resolution, no attenuation artefacts, etc.), are likely to provide insufficient information to allow a comprehensive assessment of myocardial viability if they do not consider the amount of recalcitrant dysfunctional myocardium. Clinical Scenarios, potential indications, and objectives and practical use of viability imaging in clinical practice.

In agreement with other societies and recent scientific statements,¹⁵⁵ the consensus of this group is that despite the absence of clearly documented benefits on survival observed in randomized controlled trials, viability testing remains a useful principle in clinical practice, for subacute or chronic ischaemic heart disease as well as several other emerging applications.

In *Table 4* and *Figure 12*, we present some different clinical scenarios to illustrate the potential clinical utility of viability testing. These are illustrated by case examples in *Figures 13–18*. Most often detection of myocardial viability is performed with the objective of deciding whether a patient might benefit from revascularization to improve his/her condition (*Figure 13*).



75 yo woman with acute HF, positive troponin

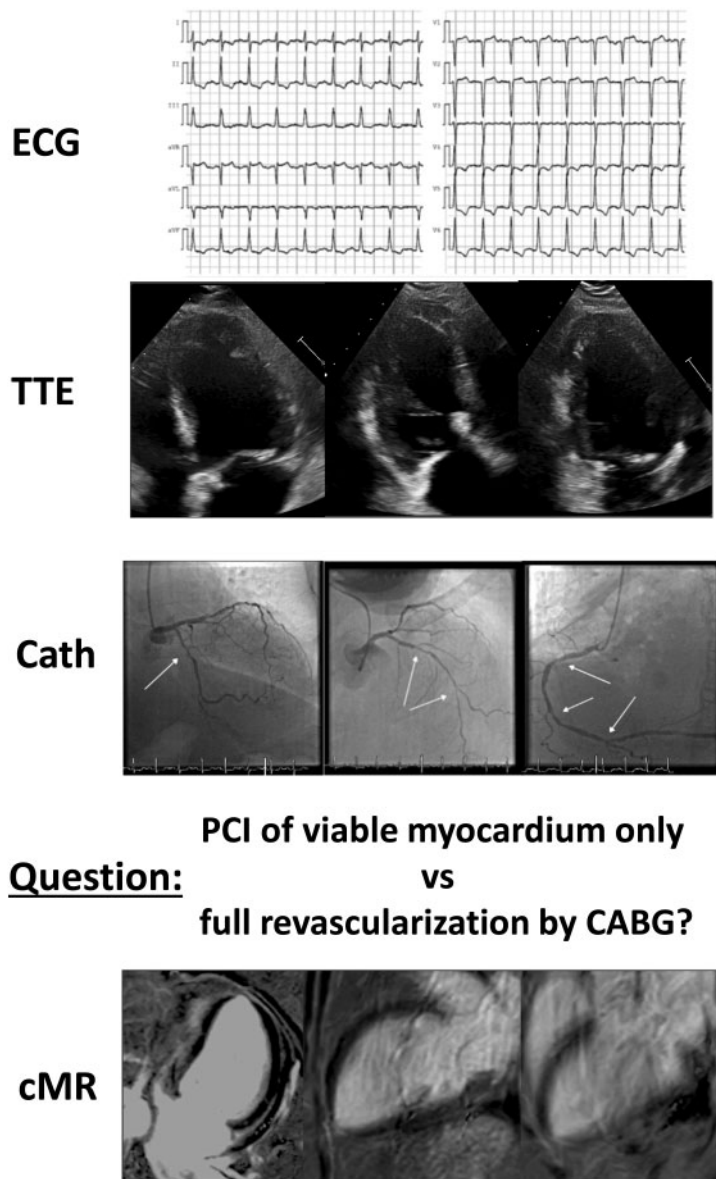


Figure 14 Illustration of the use of viability testing to select appropriate revascularization. A 75-year-old woman presenting with heart failure was found to have severe LV dysfunction on transthoracic echocardiography (LVEF 27%) with anterior, anteroseptal, and apical akinesia. Her ECG revealed Q waves in leads V1–V3. Three-vessel disease was demonstrated on cardiac catheterization with a long segment of LAD disease which was considered suboptimal for PCI, as well as localized stenosis in the right coronary artery and proximal circumflex artery, which were deemed amenable to PCI. The clinical question was to decide whether the patient should have isolated PCI to the LCX and RCA alone or whether she would benefit from bypass surgery to revascularize all coronary artery territories. LGE-CMR demonstrated complete absence of scar, and thus preserved viability in all myocardial segments. Therefore, CABG was selected as optimal revascularization technique. See also [Supplementary data](#) online, [Movie S7](#). CMR, cardiovascular magnetic resonance; LVEF, left ventricular ejection fraction; LGE, late-gadolinium enhancement.

In the 2016 ESC guidelines on heart failure¹⁵⁶ and the 2018 ESC guidelines on myocardial revascularization,¹⁵² this indication is currently only retained as a Class IIb Level B indication. It is stated that in patients with mild to moderate CAD, assessment of ischaemia may provide incremental benefit over viability. However, in patients with

extensive CAD, viability assessment may be sufficient. The clinical scenario where myocardial viability is most commonly assessed, is in patients with known coronary artery disease and reduced systolic function to select and guide revascularization (Figure 14). Management decisions in these patients are complex, with myocardial revascularization

Key point 11: clinical settings where viability may be useful

- i. Guiding the revascularization of patients with heart failure, known coronary artery disease and wall motion abnormalities (ESC recommendation Class IIB Level B).
- ii. Guiding the revascularization of patients presenting with heart failure and a late presentation acute coronary syndrome.
- iii. To select the optimal revascularization strategy in patients with complex multivessel coronary artery disease (PCI vs. CABG).
- iv. Deciding upon PCI or medical therapy in patients with chronic total occlusions (CTO).
- v. Determining the mechanism of ischaemic mitral regurgitation and guiding the decision for valve replacement and revascularization in patients with ischaemic mitral regurgitation LVEF <30% and an option for surgical revascularization (ESC recommendation Class IIA Level C).
- vi. Determining the contractile response (low-dose dobutamine echocardiography) in low-flow aortic stenosis (ESC recommendation Class IIA Level C).
- vii. Scar imaging by CMR to identify the aetiology of heart failure to distinguish between ischaemic and non-ischaemic myocardial damage in case of equivocal clinical or other imaging data in patients with dilated cardiomyopathy (ESC recommendation Class IIA Level C).
- viii. CMR Scar imaging to optimize lead positioning for CRT and to allow non-invasive substrate identification in electrophysiology planning of VT ablation (no current level of recommendation).

potentially providing benefit by allowing functional recovery. The main clinical question in these patients is whether revascularization might improve cardiac function and the patient's clinical status and whether this outweighs the potential risks of undergoing the procedure. Examples are (i) patients presenting late with heart failure a long time after their heart attack, who have an occluded coronary arteries or reduced TIMI flow in the culprit artery, where the question of late revascularization might be considered. (ii) Patients with chronic multivessel disease and wall-motion abnormalities where a decision lies between complete revascularization (potentially with CABG) including completely occluded vessels vs. a less complete procedure using PCI to selected vessels subtending viable myocardium only. (iii) Patients with a complete coronary occlusion (Figure 15) prior to undergoing complicated PCI revascularization procedures.

Other emerging clinical scenarios for assessment of myocardial viability are patients with mixed valvular and coronary artery disease. In patients with ischaemic mitral regurgitation (Figure 16), detection of myocardial viability might guide whether to revascularize the patient or proceed with mitral valve intervention (repair/replacement/Mitraclip) to improve regurgitation. Indeed the 2016 ESC HF guidelines¹⁵⁶ and the 2018 guidelines for revascularization¹⁵⁷ recommend combined valve and coronary surgery in symptomatic patients with severe secondary MR and LVEF < 30% and option for surgical revascularization (Class IIA Level C indication). Further in patients with low-flow low-gradient aortic stenosis (Figure 17), viability testing and, in particular, dobutamine echocardiography may allow assessment of whether left ventricular dysfunction is due to the valvular disease and

whether it is potentially reversible upon valve replacement (Class IIA Level C indication).

Viability testing has also been shown to predict response to CRT (Figure 18). Indeed, it has been shown that response to CRT is less likely in patients with ischaemic cardiomyopathy if scar is present in the potential target area for left ventricular stimulation (usually the postero-lateral wall).¹⁵⁸ Also scar burden by either SPECT¹⁵⁹ or CMR¹⁶⁰ was shown to predict lack of LV functional improvement and survival in CRT patients. Conversely contractile reserve by dobutamine stress echo can predict a positive CRT response.¹⁶¹ Therefore, viability assessment could also be of value in selecting patients with ischaemic cardiomyopathy and LBBB who might best respond to CRT, or alternatively to guide positioning of the left ventricular pacing lead away from regions of scarring. The 2016 ECG HF guidelines consider assessment of myocardial tissue and structure by CMR to distinguish between ischaemic and non-ischaemic myocardium (Class IIA Level C) to identify infiltrative cardiomyopathies (Class IC) and of any non-invasive imaging technique to evaluate structure and function in patients with HF who have received evidence-based pharmacotherapy before the decision on device implantation (Class IC indication). Since scar is the anatomical substrate underlying re-entry circuits, viability testing may also be of interest in patients with ventricular arrhythmias to guide ablation therapy. Infarct imaging and viability testing also allow the clinician to understand the underlying nature of the cardiac dysfunction, for instance differentiating post myocardial stunning, stress cardiomyopathy (Takutsu), myocarditis, dilated cardiomyopathy, and myocardial infarction, thereby allowing patients to receive optimal treatment for their condition. Finally, myocardial scar is associated with an adverse prognosis across a wide range of clinical condition. Scar imaging might therefore be used for *risk stratification of patients* with poor left ventricular function, and potentially to identify patients who might benefit from more aggressive therapies such as ICD implantation.

In a recent scientific statement¹⁵⁵ from the American Heart Association, two different algorithms for evaluating of patients with coronary artery disease and either chronic or subacute ischaemic LV dysfunction were proposed. It was suggested that patients with chronic ischaemic LV dysfunction should first be evaluated for possibility of revascularization, then for evidence of ischaemia. In the absence of ischaemia CMR was proposed as the first test: in patients with <25% subendocardial scar revascularization was proposed, whilst optimal medical treatment alone was suggested when scar was more transmural (>50%). In patients with 25–50% scar, metabolic (i.e. ¹⁸F-FDG PET) or contractile reserve (i.e. dobutamine echo or CMR) was proposed as the second step to decide upon revascularization. In patients with subacute LV dysfunction, the AHA proposed to evaluate first for regional LV dysfunction, then for ischaemia and to revascularize in the absence of regional dysfunction or presence of ischaemia. If regional LV dysfunction is present but no ischaemia, again testing for evidence of metabolic or contractile reserve was proposed to guide revascularization. These scenarios would therefore often call for the staged use of multiple tests, i.e. perfusion imaging followed first by LGE-CMR, and then subsequently by dobutamine CMR, stress echocardiography, or PET. This group understands the potential interest of such algorithms, but they conflict with current ESC guidelines and without newer scientific evidence on health-outcomes we cannot offer them the endorsement

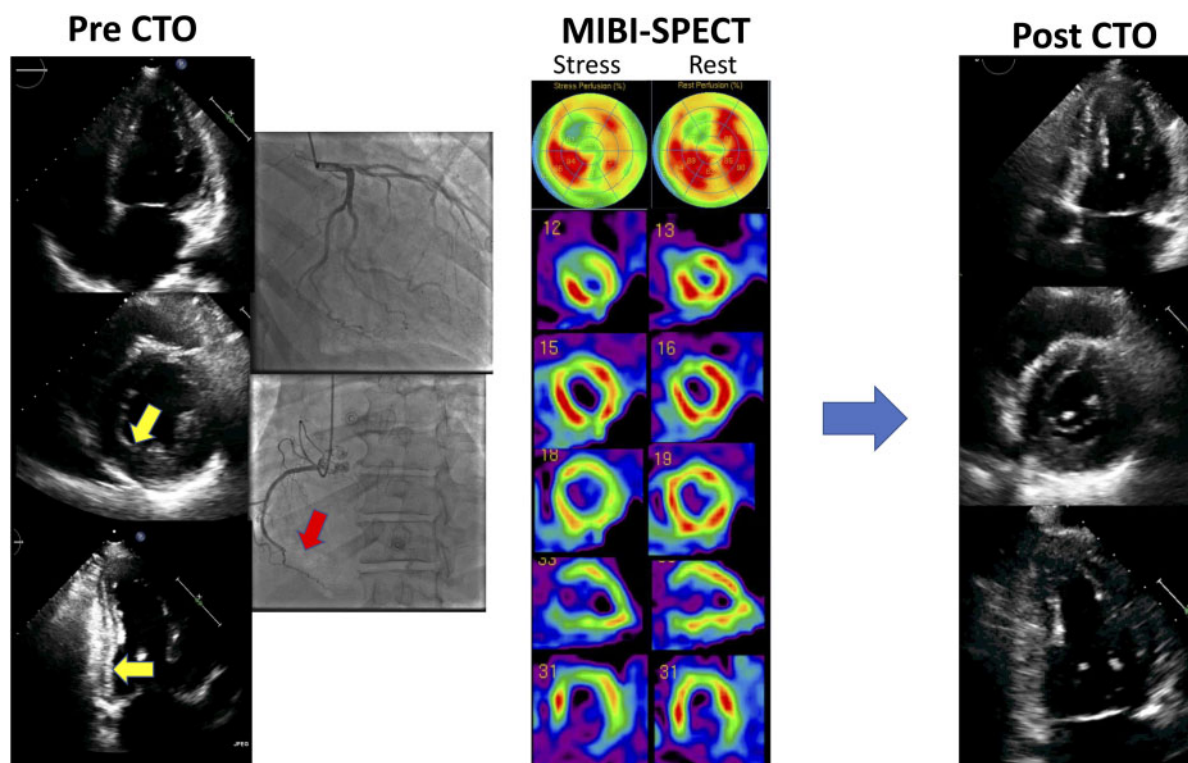


Figure 15 Example of usefulness of viability testing to guide decision making in CTO. A 65-year-old male with two episodes of acute pulmonary oedema underwent coronary angiography demonstrating occlusion of distal right coronary artery (red arrow). An echocardiogram revealed that the inferior wall was akinetic (yellow arrow). Myocardial SPECT demonstrated preserved resting perfusion indicative of myocardial viability in the inferior wall with additional exercise-induced ischaemia. The patient underwent a successful CTO procedure to reopen the right coronary artery. A followup echocardiogram performed 7 months post CTO showed improved contractility in the inferior wall. See also [Supplementary data](#) online, [Movie S8](#). CTO, chronic total occlusion; SPECT, single photon emission computed tomography.

of our group. Without any clear clinical superiority of any test, we believe that the selection of the test should be based on the clinician's preference and local experience of the centre and on which characteristics (i.e. the clinical need for high sensitivity or high specificity) are sought. We also believe that in most patients one single viability test is enough for clinical decision making. Therefore, we believe that staged tests should be used only if the first test is equivocal. For instance, functional dobutamine stress testing might be useful as second test if LGE CMR transmurality is intermediate (50%). Likewise, CMR or PET could be useful to complement dobutamine echocardiography, if image quality is suboptimal or if it is believed that the patient may not have responded due to concomitant ischaemia as for instance in the setting of total coronary occlusion⁶³ or betablocker use.

Future directions

The current trial evidence for viability imaging is scarce and published studies have important limitations including the following. PET and LGE-CMR were not included in STICH.¹⁵¹ The viability substudy of the trial classified patients dichotomously as having viable myocardium or not and did not consider viability in individual myocardial territories. Moreover, patients were not randomized based on their viability assessments. The role of percutaneous coronary intervention with respect to viability has not been the subject of large clinical

trials. Endpoints including LV end-diastolic and end-systolic volumes and LV remodelling may improve after revascularization without necessarily improving ejection fraction but have rarely been assessed.

A small number of ongoing studies aim to address some of these limitations and are expected to further clarify the role of viability imaging, in particular amongst patients with heart failure. The randomized controlled REVIVED_BCIS2 study compares percutaneous coronary intervention in addition with optimal medical therapy (OMT) with OMT alone in 700 patients with an ejection fraction of $\leq 35\%$, severe coronary disease (BCIS-1 jeopardy score ≥ 6) and viability in at least four dysfunctional segments (as assessed by DSE or CMR) amenable to revascularization by PCI.¹⁶² The primary endpoint is all-cause death or heart failure hospitalization. The Cardiovascular Magnetic Resonance GUIDEd management of mild-moderate left ventricular systolic heart failure (CMR GUIDE HF) trial is testing the hypothesis that among patients with mild-moderate heart failure, CMR-guided ICD insertion is superior to standard of care.¹⁶³

Artificial intelligence (AI) and deep learning using convolutional neural networks to process large databases of annotated medical images has generated AI algorithms that allow reporting clinicians to post-process image datasets in a fraction of the time previously taken.¹⁶⁴ The assessment of myocardial viability is complex, relying on multiple techniques, measurements, and data points. Each technique has its own limitations as already discussed but, in combination,

Decision making in ischemic Mitral Regurgitation

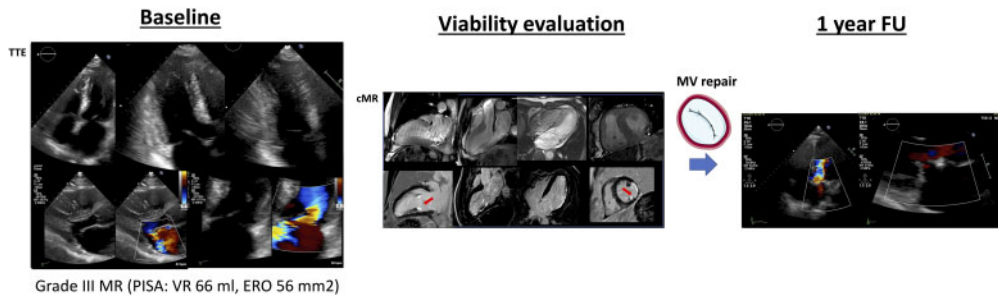


Figure 16 Example of viability imaging in ischaemic mitral regurgitation. A 49-year-old male with a history of NSTMI revascularized by PCI to the left circumflex coronary artery presented with heart failure symptoms 2 month later. Transthoracic echocardiography demonstrated severe mitral regurgitation due to restriction of the anterior leaflet (Carpentier type IIIb). LGE-CMR was performed to evaluate viability prior to mitral valve surgery and demonstrated subendocardial scar in the postero-lateral wall as well as in the inferior papillary muscle confirming the mechanism of mitral regurgitation with maintained LV function (LVEF 60%). The patient benefitted from mitral annuloplasty and valve repair without residual mitral regurgitation postoperatively. See also [Supplementary data](#) online, [Movie S10](#). CMR, cardiovascular magnetic resonance; LVEF, left ventricular ejection fraction; LGE, late-gadolinium enhancement.

Decision making in low-flow Aortic Stenosis

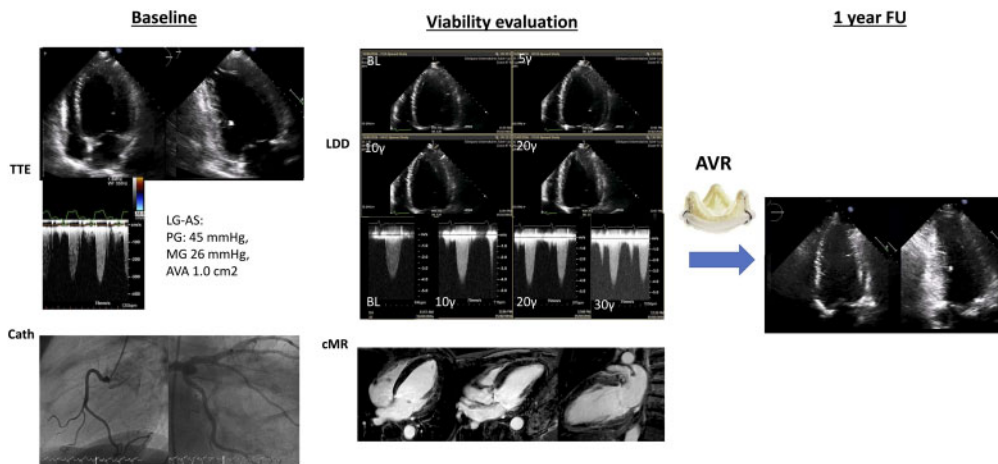


Figure 17 Illustration of usefulness of viability imaging to guide decision making in low-flow aortic stenosis. A 58-year-old male presented with acute heart failure. Echocardiography demonstrated a dilated left ventricle with severe global impairment of LV function and low-flow, low-gradient aortic stenosis (peak gradient 45 mmHg, estimated AVA 1.0 cm²). Coronary angiography did not demonstrate any obstructive coronary artery stenoses. LDD stress echocardiography up to 20 mg/kg/min was performed to evaluate further inotropic response. It demonstrated an increase in transvalvular gradient (mean gradient rose from 39 to 47 mmHg) with the valve area remaining in the borderline severe range (1.0 cm²). Contractile reserve was identified with an improvement of LVEF from 31 to 42%. LGE-CMR demonstrated the absence of scar. The patient underwent AoVR with subsequent normalization of LV function on follow-up echo (FU-TTE) and was free of heart failure symptom-free 1 year after surgery. See also [Supplementary data](#) online, [Movie S9](#). AoVR, aortic valve replacement; CMR, cardiovascular magnetic resonance; LDD, low-dose dobutamine; LVEF, left ventricular ejection fraction; LGE, late-gadolinium enhancement.

there is the potential to develop feature extraction and statistical analysis protocols with machine learning to better predict response to myocardial revascularization. Validation and testing of these datasets would typically require a large cohort of patients. However, recent advances in cardiac electromechanical modelling and image synthesis

provide the possibility of generating synthetic images based on realistic mesh simulations, a technique which is well-suited for the generation of large databases at small computational cost. Computer-aided diagnostic algorithms for the assessment of myocardial viability have been tested through the generation of large synthetic databases

Decision making in CRT

Viability evaluation

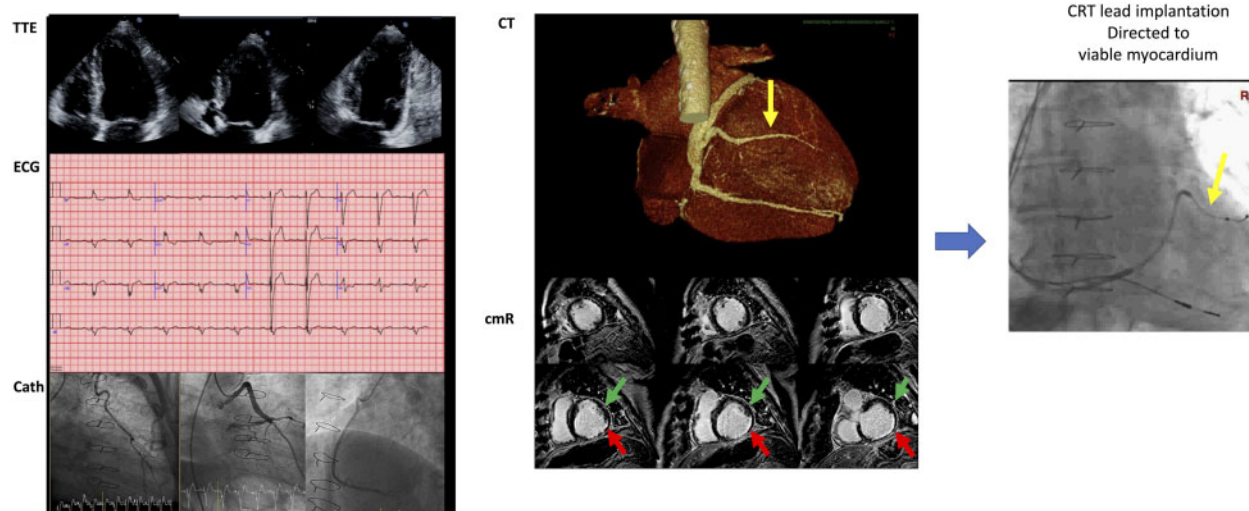


Figure 18 Illustration of use of viability testing to direct CRT lead implantation direction. A 70-year-old male presented with severe heart failure with reduced ejection fraction (LVEF 35%) and left bundle branch block on his 12-lead ECG. He had undergone coronary artery bypass surgery 10 years earlier following an inferior myocardial infarction. Coronary angiography demonstrated patent bypass grafts. LGE-CMR was performed in order to identify regions of left ventricular scar prior to CRT implantation. LGE images were co-registered with contrast-enhanced CT scanning of the cardiac veins in order to avoid lead placement into regions of non-viable scar. Scar was present in the inferior (red arrow) but not in the postero-lateral wall (green arrow). Accordingly, the LV pacing lead was implanted in a postero-lateral side branch of the coronary sinus outside of the region of scar (yellow arrow). See also Movie S11.

containing ground truth shape and motion information. By modifying the parameters of simulated meshes and images in a given zone, labelled as diseased, regional volume change from end-diastole to end-systole can be computed. This work is only at an early stage and further refinement is required before this becomes a reality in clinical practice.¹⁶⁵

Conclusions

Myocardial viability may currently be assessed clinically with three different imaging approaches: dobutamine echocardiography, nuclear Imaging (i.e. SPECT and PET) and CMR. The three techniques rely on different pathophysiological approaches to detect dysfunctional myocardium. Therefore, they reveal different aspects of dysfunctional myocardium and may detect different amounts of viable myocytes per segment. Another important limitation is that myocardial viability has so far been considered as a binary phenomenon, rather than a continuum. Because of these limitations the current diagnosis of myocardial viability is not standardized. Three large randomized controlled trials assessing the survival benefit of revascularizing viable myocardium have provided neutral results, perhaps explained by methodological limitation including recruitment bias. Nevertheless, myocardial viability and scar assessments still play an important role in clinical practice guiding revascularization decisions as well as CRT implantation and the risk stratification of patients with coronary

artery disease and other conditions. Therefore, there is a need for further work in the field to better standardize reporting of viability and explore its value in various clinical scenarios. We hope that prospective clinical trials will validate these diagnostic criteria and appropriate utilization recommendations and will support future guideline development.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: none declared.

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