Imaging

The hibernating myocardium: current concepts, diagnostic dilemmas, and clinical challenges in the post-STICH era

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Received 6 July 2012; revised 19 November 2012; accepted 3 January 2013; online publish-ahead-of-print 17 February 2013

A very large body of evidence—predominantly retrospective—suggests that revascularization is superior to optimal medical therapy in patients with a significant amount of ‘hibernating’ myocardium. Contemporary cardiological practice has embraced this standard of practice, as many centres worldwide place great emphasis upon the results of viability testing by non-invasive imaging techniques in determining the need for coronary revascularization. This practice has been challenged by the recent results of the Surgical Treatment for Ischaemic Heart Failure (STICH) trial, which suggested both lack of mortality benefit from revascularization and also from viability testing. In this review article, we have summarized the pathophysiology of hibernating myocardium, briefly discussed each of the non-invasive imaging modalities used in contemporary practice for detecting myocardial hibernation before critically appraising the prospective studies in this field, most importantly the main STICH trial and viability sub-study. STICH was clearly a complex trial but has not ended the question over the benefit of revascularization in ischaemic heart failure. Finally, we have suggested a possible methodology for an ‘ideal trial’ designed to evaluate the role of revascularization in such patients and also explored how viability testing should be used in clinical practice in the post-STICH era.

Keywords
Hibernation • Viability • Revascularization • Imaging • Ischaemic cardiomyopathy

Introduction

Concerted efforts to reduce the global burden of cardiovascular disease over the past three decades have reduced mortality from coronary artery disease (CAD) in industrialized nations. However, this has resulted in an increasing incidence of heart failure (HF), usually referred to as ischaemic cardiomyopathy (ICM). In spite of advances in pharmacological therapy and increased availability of defibrillator and cardiac resynchronization devices, both of which have come at considerable cost, the overall prognosis in ICM remains poor.

The logical assumption that chronically compromised myocardial perfusion due to CAD, in the absence of myocyte necrosis, may lead to acontractile but viable myocardium—‘hibernating myocardium’ (HM)—accrued support from decades of evidence from observational and retrospective studies. Individuals with a substantial amount of HM appeared to derive symptomatic and prognostic benefit from revascularization (which normalized perfusion) and optimal medical therapy (OMT) compared with OMT alone. Viability testing has in many centres become a gatekeeper to revascularization—the presence of a substantial amount of HM has generally been a stimulus for revascularization whereas a significant amount of scar tissue with little HM has often triggered OMT alone.

However, three prospective randomized trials—the Heart Failure Revascularisation (HEART) Trial, the PET And Recovery following Revascularisation (PARR-2) trial, and the Surgical Treatment for Ischaemic Heart Failure (STICH) trial—have challenged this concept as none found revascularization superior to OMT or found benefit for the use of viability testing in guiding management decisions or influencing mortality outcome. Each of these studies, however, had significant methodological limitations—reflecting the enormous challenges of conducting such trials—and thus there remains considerable debate about both the role of revascularization and of viability testing in ICM patients.

The objectives of this article are to provide a brief overview of the pathophysiological mechanisms of HM and the non-invasive...
methods for testing for HM, in particular highlighting their similarities and differences. We discuss the various possible definitions of response to therapy and critically appraise the STICH trial, the largest prospective randomized trial aimed at determining the value of revascularization in ICM and also the impact of myocardial viability on outcome. We have also explored how viability testing should be used in current practice following recent trial results.

Methods

To identify relevant review articles and original scientific papers, we conducted a Medline search from 1980 to 2012, using key search terms 'myocardial viability', 'viable myocardium', 'myocardial hibernation', and 'hibernating myocardium', individually and combined with the following terms: 'dobutamine echocardiography' (DbE), 'dobutamine stress echocardiography', 'thallium scintigraphy', 'technetium scintigraphy', 'Single Photon Emission Computed Tomography' (SPECT), 'positron emission tomography' (PET), 'magnetic resonance', 'cardiovascular magnetic resonance' (CMR), 'myocardial contrast echocardiography' (MCE), 'medical therapy', and 'cardiac resynchronization therapy'. Studies not published in the English language or conducted in animals were excluded.

Stunning, hibernation, and viability: a clarification of definitions

The concept of 'stunned myocardium' was first proposed 30 years ago with the observation that ischaemic insults of short duration did not cause infarction but did depress contractility, which took several days to recover ('a brief bout of ischaemia may stun the heart, but not kill it'). The terms 'viable' and 'hibernating' myocardium have previously been used interchangeably in the literature with potential for confusion. Some authors advocated that 'viability' be used prospectively to define myocardium which is dysfunctional at rest but not scarred and therefore has the potential for functional recovery, whereas 'hibernation' should be used retrospectively only to describe those segments which actually improve following revascularization. Since HM must, by definition, also be viable, in this article we refer to dysfunctional but viable myocardium as HM.

Mechanisms of hibernation and implications for imaging

The ‘smart heart hypothesis’—the deliberate reduction in myocardial contractility and cellular activity to minimize metabolic demands in the face of severely reduced myocardial blood flow (MBF)—generated the conventional paradigm that stunned myocardium and HM are both dysfunctional at rest, but the former has normal resting MBF whilst the latter has reduced resting MBF. The pathophysiological triad that characterizes HM is thus reduced MBF and MBF reserve, presence of a flow-limiting (i.e. ischaemia-inducing) coronary artery stenosis subverting the dysfunctional myocardium and evidence that this myocardium is not irreversibly damaged (i.e. is ‘viable’ or ‘recoverable’). Animal and human studies have shown that stunned and HM often co-exist—biopsies from stunned myocardium (defined by PET as normal perfusion and metabolism) show less-severe cellular structural changes than biopsies from HM (defined by PET as reduced perfusion with maintained metabolism). It is now widely believed that repetitive episodes of stunning (i.e. myocardial ischaemia) lead to development of HM. Thus stunning and hibernation are likely to be part of a continuous disease spectrum with stunning a less-severe form of dysfunction and, consequently, more likely to recover function following revascularization. However, HM cannot maintain viability indefinitely and delayed revascularization is associated with worse outcome. The time period after which a patient is re-studied following revascularization is also of importance, as recovery of HM may take several months and thus premature assessment may ‘miss’ subsequent functional recovery.

Identification of hibernating myocardium

Data extracted from a pooled analysis showing the sensitivities and specificities of the various imaging modalities are presented in Table 1. Using the same inclusion/exclusion criteria, we have added data for MCE. There are significantly fewer studies, with very small patient numbers, that assessed global functional recovery and thus only data for regional recovery is presented.

Comprehensive overviews of the roles of echocardiography, CMR, and PET in the assessment of HM have recently been published. However, it is pertinent to highlight the more fundamental differences between these modalities. Single photon emission computed tomography, late gadolinium-enhancement CMR (LGE-CMR), and MCE assess cellular integrity, PET assesses cellular metabolism (thus also cellular integrity), and dobutamine techniques (echocardiography or CMR) assess contractile reserve—therefore, it is unsurprising that, in practice, these tests can yield conflicting results. As mentioned above, techniques that detect presence (SPECT, PET, MCE) or absence (LGE-CMR) of cellular integrity are likely to be more sensitive but less specific than techniques that detect contractile reserve (DbE and Db-CMR) because a critical myocardial mass needs to be viable for a functional response to occur. Furthermore, there are technical differences amongst the imaging modalities; for example, SPECT has the lowest spatial resolution compared with other available techniques and this may affect its diagnostic accuracy. Additionally, exposure to ionizing radiation may also play a role in the technique chosen.
The most commonly used echocardiographic technique is DbE. Low-dose dobutamine can augment myocardial thickening and thus elicit contractile reserve, although at higher doses the residual coronary flow reserve is exhausted and can thus trigger ischaemia—this ‘biphasic response’ is considered the best indicator of likelihood of functional recovery after revascularization. Deformation imaging, such as tissue Doppler imaging and speckle tracking echocardiography, provides objective quantifiable indices of regional myocardial function, namely strain and strain rate. Contrast echocardiography is widely used clinically to assess myocardial wall motion and thickening and, furthermore, it can also assess micro-circulation integrity, which reflects cellular integrity, and thereby distinguishes HM from scar tissue. Myocardial contrast echocardiography is also used for the qualitative and quantitative assessment of myocardial perfusion. Finally, significant wall thinning (end-diastolic wall thickness ≤6 mm) due to myocyte necrosis, with hyper-echoic myocardium—reflecting fibrosis—is usually associated with irreversible loss of myocardial tissue and has an extremely high negative predictive value for functional recovery (although specificity is lower). In summary, in an echocardiography laboratory today, a combination of modalities is used for optimal detection of HM—for example, lack of contractile reserve in a segment >6 mm thickness with preserved perfusion by MCE points towards HM.

Figure 1  Spectrum of myocardial dysfunction in ischaemic cardiomyopathy. (A) Stunned myocardium more likely to recover function if revascularized (green arrow). (B) Hibernating myocardium demonstrates more advanced cellular degeneration and thus less likely to recover function after revascularization (orange arrow). Boxes on the left side illustrate the pathophysiological responses seen at each stage. CFR, coronary flow reserve; CR, contractile reserve; MET, metabolism; PERF, perfusion; SCAR, scar or fibrosis; ✓, present; ↔, equivocal response; x, absent.

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Thallium-201 (Tl-201), a potassium analogue, is actively transported into cardiomyocytes and this dependence upon intracellular intake allows it to act as a tracer of viability. Several protocols have been validated for the detection of HM including rest-redistribution, stress-redistribution, and late-reinjection, and late-gadolinium enhancement (LGE-CMR). In contrast to Tl-201, cellular uptake of Technetium agents sestamibi and tetrafosmin is predominantly passive, although intracellular retention requires mitochondrial uptake which is an active process. Previous studies have suggested equivalence between the two techniques and, currently, no technique can claim ‘gold standard’ status for the assessment of HM.

Positron emission tomography is the most advanced form of nuclear imaging, with superior resolution to SPECT. The PET scanner visualizes the temporal and spatial distribution of tracers labelled with positron-emitting radionuclides. In HM, to preserve energy, energy-requiring fatty acid metabolism switches to energy-efficient glucose metabolism. Fluorodeoxyglucose (FDG) uptake reflects the presence of glucose metabolism. Preserved FDG uptake is a pre-requisite for viable tissue and the combination of preserved tracer uptake with reduced MBF (perfusion-metabolism mismatch) is considered the hallmark of HM, whereas the absence of tracer uptake and reduced perfusion (perfusion-metabolism match) reflect scar tissue. The major limitation of cardiac PET is its restricted availability.

The two most widely used CMR techniques are dobutamine CMR (Db-CMR) and late-gadolinium enhancement (LGE-CMR). Db-CMR is less favoured in many units as it takes longer to scan patients, the tachycardia and/or ectopies induced by dobutamine can degrade image quality and management of patients who develop ventricular arrhythmias, or severe chest pain is complicated as they are within an electromagnetic field. Cardiovascular magnetic resonance detects myocardial necrosis and fibrosis through the use of gadolinium-based extracellular contrast agents. The distribution of the contrast agent is in proportion to the extracellular space, which is increased during acute necrosis and chronic fibrosis. Imaging is performed more than 10 min after contrast injection to allow the distribution of the contrast agent into the infarct and to reach a semi-steady state. The transmural extent of infarction (TEI) is then visually estimated—most units use a cut-off of >50% TEI for non-viable myocardium.

Importantly, the cut-off value of TEI used directly influences the technique’s accuracy. As the cut-off value for TEI increases, the sensitivity for predicting recovery falls but specificity rises. For example, >75% TEI has a 100% negative predictive value for functional recovery after revascularization. However, in patients with <75% TEI, the additional assessment of contractile reserve by Db-CMR improves predictive accuracy over LGE imaging alone. The principal limitations of CMR are its contra-indication in patients with implanted ferro-magnetic objects (e.g. pacemakers and defibrillators), potential for claustrophobia, and risk of contrast-induced toxicity in those with pre-existent significant renal dysfunction [patients with Stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate < 30 mL/min) are usually not given gadolinium].

Finally, failure of a dysfunctional but viable myocardial segment to recover function following revascularization does not necessarily imply an error in the test as recovery is affected by a number of factors, as outlined in Figure 2.

### Table 1 Comparison of the various imaging techniques for detecting hibernating myocardium

<table>
<thead>
<tr>
<th>Technique</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Mean EF (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine echocardiography—total</td>
<td>41</td>
<td>1421</td>
<td>25–48</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Low-dose DbE</td>
<td>33</td>
<td>1121</td>
<td>25–48</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>High-dose DbE</td>
<td>8</td>
<td>290</td>
<td>29–38</td>
<td>83</td>
<td>79</td>
</tr>
<tr>
<td>Myocardial contrast echocardiography—total</td>
<td>10</td>
<td>268</td>
<td>29–38</td>
<td>87</td>
<td>50</td>
</tr>
<tr>
<td>Thallium scintigraphy—total</td>
<td>40</td>
<td>1119</td>
<td>23–45</td>
<td>87</td>
<td>54</td>
</tr>
<tr>
<td>Tl-201 rest-redistribution</td>
<td>28</td>
<td>776</td>
<td>23–45</td>
<td>87</td>
<td>56</td>
</tr>
<tr>
<td>Tl-201 re-injection</td>
<td>12</td>
<td>343</td>
<td>31–49</td>
<td>87</td>
<td>50</td>
</tr>
<tr>
<td>Technetium scintigraphy—Total</td>
<td>25</td>
<td>721</td>
<td>23–54</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td>Without nitrates protocol</td>
<td>17</td>
<td>516</td>
<td>23–52</td>
<td>83</td>
<td>57</td>
</tr>
<tr>
<td>With nitrates protocol</td>
<td>8</td>
<td>205</td>
<td>35–54</td>
<td>81</td>
<td>69</td>
</tr>
<tr>
<td>Positron emission tomography—total</td>
<td>24</td>
<td>756</td>
<td>23–53</td>
<td>92</td>
<td>63</td>
</tr>
<tr>
<td>Cardiovascular magnetic resonance—total</td>
<td>14</td>
<td>450</td>
<td>24–53</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Low-dose dobutamine protocol</td>
<td>9</td>
<td>272</td>
<td>24–53</td>
<td>74</td>
<td>82</td>
</tr>
<tr>
<td>Late gadolinium-enhancement protocol</td>
<td>5</td>
<td>178</td>
<td>32–52</td>
<td>84</td>
<td>63</td>
</tr>
</tbody>
</table>

Ischaemia vs. viability: are they equally important?

As mentioned above, by definition dysfunctional myocardium in ICM must be ischaemic to be labelled ‘hibernating’. Therefore, intuitively, one would expect that ischaemia should be demonstrable and of clinical value in all such patients; however, there is a considerable variation amongst prior studies that examined whether it is necessary to assess both viability and ischaemia or whether viability testing alone is sufficient in ICM patients.
Several studies have shown that, in those with documented CAD at angiography, assessment of regional myocardial viability alone identifies the patients who experience functional and prognostic benefit from revascularization. Furthermore, the published data on the relative merits of ischaemia testing in ICM are also inconsistent. The biphasic response during DbE—a marker of both viable and ischaemic myocardium—was the best predictor of regional functional recovery in one study but did not add incremental value over viability status in a different study.

However, closer scrutiny reveals the reasons for these apparent discrepancies. In the studies in which ischaemia did predict outcome, the patients generally had less severe CAD (e.g. 46, 35, and 50% patients had 3-vessel disease in three studies that examined this specific issue), whereas in the studies in which ischaemia did not provide incremental information over viability status, patients had more extensive CAD (e.g. 85% patients had 3-vessel disease in one study with 5-year follow-up). The implication, therefore, is that in those patients with severe (i.e. flow-limiting) CAD—defined as ≥75% coronary stenoses in the three major coronary arteries and with one or more occluded arteries—only demonstration of myocardial viability is necessary whereas in all patients with mild or moderate CAD, testing for ischaemia is also required.

The heterogeneity in the evidence base is reflected in the 2010 ESC guidelines on myocardial revascularization, which recommend viability testing in patients with ischaemic HF but do not state that it is necessary to demonstrate inducible ischaemia as well. It is against this background of clinical evidence and practice guidelines that we suggest testing for both viability and ischaemia in patients (whose predominant symptom is dyspnoea) with LV dysfunction and mild–moderate CAD. However, for patients with severe (multi-vessel) CAD, viability testing alone should suffice.

What constitutes ‘benefit’ from therapy?
Response to therapy may be judged in several ways, as illustrated in Figure 3.
Improvement of functional status

Functional status can be determined subjectively using NYHA class and quality-of-life (QoL) questionnaires or objectively using cardio-pulmonary exercise and/or 6-min walk testing. Although improved QoL is more important to patients than reverse remodelling or increased ejection fraction (EF), patient-centred outcomes are usually secondary endpoints in trials as they are highly subjective and more susceptible to confounding due to a placebo effect. Additionally, the change in the functional class often correlates weakly with the change in exercise capacity, the change in EF and with degree of HM, such that functional improvement is often unpredictable.50

Improvement of left ventricular ejection fraction

There is conflicting evidence about whether improvement of left ventricular ejection fraction (LVEF) translates into improved survival in ICM, with some studies finding that EF improvement following revascularization is associated with fewer cardiac events40,45,51 and other studies reporting no mortality difference between those with and without EF improvement.52,53 It is important to note that failure of resting EF to improve following revascularization is not proof of non-viable myocardium. Studies have demonstrated that although rest EF remains unchanged, stress EF (in response to dobutamine) improves similarly between patients that do and do not have improved resting EF (≥5%) after revascularization, implying that resting EF alone may not be sufficient to evaluate successful revascularization.54

Improvement of left ventricular geometry

Chronic myocardial hypoperfusion causes ventricular remodelling (dilatation); severely dilated ventricles often do not improve in function following revascularization, irrespective of the quantity of HM, whilst reverse remodelling (reduction in ventricular volumes) following revascularization is associated with improved prognosis.55–57

Additionally, subendocardial scar can prevent systolic thickening at rest, but revascularization of the mid-myocardial and epicardial layers—which maintains their viability—helps prevent scar expansion58 and, consequently, even though segmental contractile recovery may not occur, the absence of further cavity dilatation is in fact a benefit of revascularization.56

Reduction in arrhythmic events

Scar burden, ischaemia, and depressed LV contractility are important substrates for electrical instability. Revascularization should relieve myocardial ischaemia, which may therefore decrease the arrhythmic potential.59 Although revascularization does reduce sudden cardiac death (SCD) in ICM,60 the recurrence rate of ventricular arrhythmias remains high.61 Additionally, although the majority of ICM patients undergo revascularization prior to ICD implantation, many patients nonetheless receive appropriate shocks. Furthermore, ICDs dramatically reduced mortality in primary prevention trials,62,63 implying that the risk of SCD remains high despite revascularization. It is thus likely that revascularization modifies the triggers of arrhythmias (e.g. ischaemia) with less effect upon the substrate (e.g. scar).
The evidence for revascularization in ischaemic cardiomyopathy

The term revascularization has widely been used in ICM but rarely defined. Ideally, revascularization in ICM refers to treatment not only of dysfunctional but viable myocardium but also of remote, normally contracting myocardium (at rest) but subtended by flow-limiting stenoses. Ten years ago, a meta-analysis comprising 24 studies reported patient survival using Ti-201 SPECT (n = 6), FDG-PET (n = 11), or DbE (n = 8) to assess HM.3 A strong association between the presence of HM and improved survival after revascularization was noted—in patients with HM, revascularization was associated with an 80% reduction in annual mortality compared with OMT (16 vs. 3.2%) whereas, in those without HM, there was no difference in outcomes irrespective of management strategy. As a result, thereafter some even questioned whether it would be ethical to randomize ICM patients (to OMT) in future studies.6 However, the studies were observational, non-randomized, unblinded, subject to many sources of bias and displayed enormous methodological heterogeneity (see Supplementary material online, Table S1). Therefore, it becomes difficult to draw definitive conclusions from this pooled data.

Consequently, the need for prospective studies to (attempt to) settle the issue of revascularization and viability testing in ICM was clear. Importantly, the three published prospective studies to date (HEART, PARR-2, and STICH) each addressed a slightly different clinical question (see Table 2). In summary, the HEART trial terminated prematurely (only 138 of 800 patients recruited) due to lack of funding and preferential enrolment into the STICH trial4 and was not sufficiently powered to draw conclusions. In the PARR-2 study, although ICM patients were randomized to receive either standard care or management guided by PET imaging,5 25% patients in the PET arm did not receive the recommended strategy and thus the study did not demonstrate a benefit from PET-guided management, although analysis of only those patients that did adhere to the PET-guided recommendations did reveal a significant mortality benefit.5

The Surgical Treatment for Ischaemic Heart Failure trial: a critical appraisal

Following the inconclusive results of the HEART and PARR-2 studies, the STICH trial results were eagerly anticipated. The trial had a complex design (Figure 4) as it aimed to answer three outstanding issues: first the added value of revascularization over OMT (hypothesis 1),6 secondly the benefit of adding surgical ventricular reconstruction (SVR) to CABG (hypothesis 2)65 and thirdly the impact of determining myocardial viability prior to revascularization.7

The results of hypothesis 1 showed no mortality benefit of revascularization over OMT and the viability sub-study found that viability testing did not alter outcomes (irrespective of management strategy). The STICH trial has already generated significant controversy. Strong criticism of the trial’s methodology66 has been met with robust rebuttals from the trial’s steering committee.67 It is important to highlight both the strengths and weaknesses of the study. In comparison with prior studies, STICH was a well-designed trial. Oversight committees ensured that optimal therapies were used in each group and surgeons were required to demonstrate surgical expertise in ICM patients (previous operative mortality <5%). Patients assigned to CABG underwent surgery at a median time interval of just 10 days after randomization. Finally, and impressively given the size of the study, <1% patients were lost to follow-up.

However, there were some key factors that may have influenced the trial results. First, the demographics of the enrolled patients are important—the mean age was just 60 years, >60% predominantly suffered angina pectoris and >60% were in NYHA class I or II HF. Thus, the STICH trial was a study in CAD patients with LV dysfunction and angina rather than patients with HF syndrome per

### Table 2 Summary of the HEART, PARR-2, and STICH trials

<table>
<thead>
<tr>
<th>Study feature</th>
<th>HEART</th>
<th>PARR-2</th>
<th>STICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>138</td>
<td>430</td>
<td>1212</td>
</tr>
<tr>
<td>Countries/sites</td>
<td>1/13</td>
<td>2/9</td>
<td>22/99</td>
</tr>
<tr>
<td>Clinical question</td>
<td>Is REV superior to OMT with significant HM?</td>
<td>Is imaging-guided care superior to standard care in ICM?</td>
<td>Is REV superior to OMT in patients with ICM?</td>
</tr>
<tr>
<td>Baseline LVEF (%)</td>
<td>24</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Imaging techniques</td>
<td>DbE, PET, SPECT</td>
<td>PET</td>
<td>DbE, SPECT</td>
</tr>
<tr>
<td>Revascularization</td>
<td>CABG/PCI</td>
<td>CABG/PCI</td>
<td>CABG only</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>12</td>
<td>56</td>
<td>No benefit of REV over OMT</td>
</tr>
<tr>
<td>Result</td>
<td>No significant benefit of REV over OMT</td>
<td>No difference between PET-guided care and standard care</td>
<td>Numerous potential confounding factors affecting both the main trial and viability sub-study</td>
</tr>
<tr>
<td>Key caveat</td>
<td>Severely underpowered (only recruited 138 of intended 800 patients)</td>
<td>25% patients did not adhere to recommended management based on PET findings</td>
<td></td>
</tr>
</tbody>
</table>

REV, revascularization.
se because the presence of clinical HF was not necessary for trial enrolment.68

Secondly, several investigators previously admitted difficulty in recruitment.69 Many cardiologists already had preconceptions about the ‘correct’ management of such patients and were reticent to put their patients forward for randomization, which introduced a selection bias. Indeed, the average recruitment rate was just two patients per site per year, strongly suggesting that many eligible patients were not enrolled. This was especially true for patients considered good candidates for CABG (the outcome of patients screened but not subsequently enrolled was not reported), and many of whom were operated on without inclusion in the trial, thus potentially biasing the results against CABG.

Thirdly, the trial excluded patients with significant left main stem disease given the proven prognostic benefit of CABG in such
patients—their exclusion may well have removed benefit that might otherwise have been seen in the revascularization group. Fourthly, the cross-over rate between groups was not insignificant. Seventeen per cent of patients assigned to OMT actually underwent CABG and 9% of patients randomized to CABG never underwent surgery. Furthermore, 37 patients (6%) in the OMT group underwent PCI, conferring the potential to relieve resting ischaemia and thus improve the outcome, but this was not counted as revascularization. Therefore, although the intention-to-treat analysis did not demonstrate a beneficial impact of revascularization, the as-treated analysis did show significant benefit for CABG over OMT alone ($P < 0.001$). Finally, although a key inclusion criterion was LVEF $< 35%$, Core Lab analysis of the resting echocardiograms showed that, in fact, almost one-fifth (18.5%) of patients had an EF of $>35$ and $8$% had an EF of $>40%$.

The viability sub-study of STICH has generated even greater debate and its methodology also deserves scrutiny. First, this was not a true randomized assessment as only half of the patients (601 of 1212) underwent viability testing, which was left to the discretion of the responsible cardiologist. It is highly likely that many patients who demonstrated HM were not randomized and underwent revascularization and that those without HM also were not enrolled (only 19% of STICH trial patients had no demonstrable HM).

Secondly, patients who underwent viability testing had significantly greater LV dysfunction, LV dilatation, and incidence of previous AMI. It is known that patients with very severe LV dysfunction and also severely remodelled ventricles are less likely to benefit from revascularization. This is therefore a crucial difference between the groups and made it more likely that viability testing would appear ineffective.

Thirdly, the initial study protocol included SPECT as the only form of imaging but, due to slow recruitment, the protocol was amended 2 years into the study to allow incorporation of DbE as another technique. CMR and PET imaging were not evaluated in the STICH trial. The definitions of ‘viability’ were significantly different between the techniques—for DbE, $≥ 5$ segments with contractile reserve constituted viability whereas for SPECT, $≥ 11$ segments with preserved tracer uptake constituted viability. Furthermore, the SPECT protocol examined tracer defect size without assessing the relationship between perfusion and resting wall motion and therefore did not truly evaluate the viability of dysfunctional segments. Additionally, ischaemia as well as viability was not tested in most patients. Finally, as all these patients were drawn from the main STICH trial, it is questionable whether the sub-study could be positive if the results of the main trial (hypothesis 1—revascularization vs. OMT) were negative.

In Figure 5, we propose a possible protocol for a prospective study designed to clarify whether revascularization of patients with significant HM is beneficial compared with OMT. The key clinical question is whether viability testing (to decide treatment strategy based on the presence or absence of HM) influences patient survival and thus the primary endpoint is all-cause mortality. As there are no contemporary comparative studies indicating that one modality is superior to another, our protocol allows the use of DbE, SPECT, or CMR—clinically the three most commonly used techniques—for assessing viability and ischaemia. The cut-offs suggested for the presence or absence of HM ($≥ 5$ segments) and ischaemia ($≥ 3$ segments for DbE and $>10$% myocardium for SPECT and CMR) are based on previous studies, although various different values have been published to date and, for ischaemia, the values are extrapolated from studies in patients with normal LV function (as there is a dearth of evidence regarding the accuracy of imaging techniques to detect ischaemia in ICM patients). All patients would undergo imaging and, thereafter, patients with significant HM would be randomized whereas patients without significant HM would receive OMT only. Post-treatment, all patients would be followed-up to assess the change in functional status, LV geometry, and function, and for survival.

**What are the alternatives to revascularization in ischaemic cardiomyopathy?**

In spite of surgical, technological, and pharmacological advances, revascularization carries greater risks in ICM patients and these must be balanced against the putative benefits. All ICM patients should receive standard pharmacological therapy for HF, as per current recommendations. However, a high mortality rate persists in the medically managed ICM population.

Cardiac resynchronization therapy (CRT), in comparison with OMT, reduces mechanical dysynchrony and ventricular volumes, decreases severity of mitral regurgitation, increases LVEF, improves QoL, and reduces mortality in patients with HF but to a lesser extent in ICM than non-ICM patients. The response to CRT is proportional to the degree of HM and, additionally, scar in the posterolateral wall (over which the LV lead is usually positioned) prevents echocardiographic and clinical response to CRT.

A recent intriguing study randomized ICM patients to CABG alone or CABG with simultaneous epicardial CRT implantation and found a significantly lower mortality in the latter group (10 vs. 26%) at a 18-month follow-up, but these findings require confirmation in larger multi-centre studies before such an approach can be widely advocated.

**The ‘Ideal Trial’: could it ever be ‘ideal’ from all perspectives?**

The widespread attention given to the methodological limitations of the STICH trial inevitably raises the intriguing question of what methodology would be used in an ‘ideal’ trial in ICM. The challenges faced by previous investigators have revealed the numerous difficulties in conducting such studies. Could an ‘ideal trial’ be completely free of bias?

**What is the role of viability testing in clinical practice post-Surgical Treatment for Ischaemic Heart Failure?**

Based on the above discussion, and consistent with the ESC 2010 guidelines on myocardial revascularization, an algorithm
for integrating non-invasive imaging into contemporary ICM management is suggested in Figure 6. The current role of viability testing remains the prediction of potential functional and clinical improvement in patients with impaired LV EF, thereby facilitating a better estimate of the potential benefit of revascularization therapy, vs. its risks. Therefore, it can help patients and

**Figure 5** Proposed methodology for the ‘ideal trial’ to define the impact of viability and ischaemia testing in ischaemic cardiomyopathy, CR, contractile reserve.
physicians to make better choices about therapies which could potentially improve their functional status, even if currently we do not have robust evidence that they may improve their survival.

**Conclusions**

In spite of decades of research, the management of patients with HM remains challenging and there are still many unanswered questions. From a clinical perspective, the presence and magnitude of HM, degree of LV remodelling, timeliness, and completeness of revascularization, optimization of medical therapy, and associated co-morbidities all can affect the outcomes. Nevertheless, in 2012, testing for HM continues to be requested and performed in ICM patients being considered for revascularization.

None of the imaging modalities boast optimal accuracy for predicting regional or global functional recovery, improvement of patient symptoms, or improved survival. Additionally, as none of the imaging tests have been shown to be significantly different from one another for the prediction of HM, local expertise, cost, risks, and availability should dictate the technique utilized. In the absence of definitive prospective data, it is likely that cardiologists will continue to rely on the existing evidence base to guide

**Figure 6** Algorithm suggesting how to integrate viability (V) and ischaemia (I) testing into contemporary clinical practice. Patients with predominant angina are on the left side, those with predominant dyspnoea on the right side. In dyspnoeic patients at high risk of revascularization, but who remain symptomatic despite OMT + CRT, viability testing should also be performed before deciding on revascularization.
Supplementary material

Supplementary material is available at European Heart Journal online.

Funding

Conflict of interest: none declared.

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