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The current role of viability imaging to guide revascularization and therapy decisions in patients with heart failure and reduced LV function.

Short title: Viability testing in heart failure patients.

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Abstract

This review describes the current evidence and controversies for viability imaging to direct revascularization decisions and the impact on patient outcomes. Balancing procedural risks and possible benefit from revascularization is a key question in patients with heart failure of ischemic origin (IHF). Different stages of ischemia induce adaptive changes in myocardial metabolism and function. Viable but dysfunctional myocardium has the potential to recover after restoring blood flow. Modern imaging techniques demonstrate different aspects of viable myocardium; perfusion (SPECT, PET, CMR), cell metabolism (PET), cell membrane integrity and mitochondrial function (201Tl and 99mTc-based SPECT), contractile reserve (stress echocardiography, CMR) and scar (CMR). Observational studies suggest that IHF patients with significant viable myocardium may benefit from revascularization compared to medical treatment alone but that in patients without significant viability, revascularization appears to offer no survival benefit or could even worsen the outcome. This was not supported by 2 randomized trials (STICH and PARR-2) although post-hoc analyses suggest that benefit can be achieved if decisions had been strictly based on viability imaging recommendations. Based on current evidence, viability testing should not be the routine for all patients with IHF considered for revascularization but rather integrated with clinical data to guide decisions on revascularization of high-risk patients with comorbidities.

Introduction

Despite recent advances in the treatment of cardiovascular disease, heart failure (HF) continues to cause significant morbidity and mortality, driven by coronary artery disease (CAD) in 2/3 of HF patients.⁽¹⁾ The challenge is to define which patients with HF of ischemic origin (IHF) will benefit from a strategy of revascularization in addition to guideline directed medical therapy (GDMT) which is the mainstay of treatment in these patients.

Fundamental concepts regarding viability imaging

In patients with IHF, left ventricle (LV) dysfunction can result from scar, stress-induced ischemia, resting ischemia, remodelling, stunning, hibernation or a combination of these processes. To understand the potential benefits of revascularization, knowledge of the different myocardial states in IHF is essential.⁽²⁻⁷⁾

Myocardial ischemia refers to a state of inadequate oxygen delivery that cannot meet the myocardium's metabolic demand.⁽⁸⁾ The severity of inadequate flow will determine the intrinsic molecular adaptations of the myocardium and

accounts for both the time course and the extent of reversibility after a successful revascularization.(8)

Dysfunctional but viable myocardium develops as an adaptation to ischemia of varying degrees of severity and duration (after acute, subacute or persistent perfusion deficits) not severe enough to cause cell death.(3) The resting contractile function is altered but the myocytes are still alive and cell dysfunction can be reversed after coronary flow is restored. Three types of response can occur and present a partially overlapping continuum; remodelling, stunning and hibernation (Table 1).

Myocardium in jeopardy refers to ischemic and/or viable tissue.

Non-viable myocardium i.e scar occurs when cell death is irreversible and non-contracting [fibrotic] tissue replaces the normal myocardium. Scar can be transmural or involve only part of the wall thickness.

Viability testing aims to prospectively differentiate scar from jeopardized myocardium that has the potential to recover after revascularization.

Clinical evidence for viability testing

Although there exists an abundance of non-randomized data that suggests the presence of viability can define patients likely to benefit from revascularization, (3,16-19)(20) randomized studies to date have not demonstrated statistically significant differences.(4,16,21-23) There is some observational data to suggest that the extent of hibernating myocardium can predict the likelihood of outcome benefit or recovery; (5,24-27) and post-hoc RCT data that observed: if there is adherence to imaging based recommendations, there may be outcome benefit.(4,16,28)

Revascularization carries inherent upfront risks of mortality and morbidity, which are more pronounced in patients with HF. When revascularization is considered in patients with IHF, two important questions arise: first, does revascularization benefit these patients with severe HF; and second, is viability testing of additional value in decision making?

The STICH extension study showed a long-term (10 year) survival benefit from CABG compared to optimal medical therapy (OMT) in patients with LV dysfunction and target vessels suitable for revascularization.(29) However, given the conflicting and scarce evidence,(21,30) revascularization is not necessarily the treatment of choice for all. This is where viability testing might be beneficial. A multitude of observational studies suggest the presence of viable myocardium results in better recovery in LV function (3,17,25,31) and survival after revascularization.(3,16,17,24,26) Further, studies have shown that the extent of viability correlates with the magnitude of improvement in HF symptoms post surgery (25,27) and that PET guided management results in improved quality of life.(32) However, these results are not consistent accross studies.(22,33,34)

Many prior studies are limited by retrospective design with possible selection bias and many predate the use of current evidence-based medications. Six meta-analyses of this topic have been published since 2002.(3,18,19) Their findings were that the beneficial effect of revascularization is largely dependent on the presence of myocardial viability. From Orlandini et al., 32 non-randomized studies with 4328 patients and 4 randomized studies with 1079 patients were combined.(19) The results from non-randomized studies suggested significant mortality benefit from revascularization only in patients with viability. However no mortality benefit from revascularization was evident in the 4 randomized studies, leaving the overall interpretation of these results inconclusive.

There are two large randomized studies to address the question of viability testing in revascularization. PARR-2 (The PET and Recovery Following Revascularization) was the first study designed to answer to this question.(4) 430 patients with LVEF $\leq 35\%$ from 9 centers were randomized to either viability assessment with 18FDG-PET or standard care without PET. There was a trend towards benefit for the primary outcome (cardiac death, myocardial infarction and cardiac hospitalization) at 1 year in the PET arm. However, not all the patients were treated according to what the imaging findings recommended. In a post-hoc analysis, a significant reduction in outcomes was observed in the PET arm (HR 0.62; $p=0.019$) in the cohort in whom management decisions adhered to the imaging recommendations (75% of cases). Long-term (5 years) follow-up showed similar findings (HR 0.73; $p=0.042$). (16)

The importance of expert image interpretation and subsequent clinical decision making were highlighted in the Ottawa-5 substudy: 111 patients from an experienced center with interpretation expertise and easy access to FDG-PET.(28) In this scenario, patients in the PET arm had a clear benefit when compared to standard care (19% versus 41%) at 1 year (HR 0.34; $p=0.005$). In addition, the amount of hibernating myocardium plays an important role in patient outcome (**Figure 1S Supplementary data**). Ling et al showed with increased extent of mismatch (hibernating myocardium), the likelihood of benefit with revascularization also increased.(24) In a PARR-2 substudy a cut-off of 7% distinguished patients who would or would not benefit from revascularization.(5) Similar cut-offs of 5-10% have been found in other studies.(24,25)

In the STICH (Surgical Treatment for Ischemic Heart Failure) trial (22), 1212 patients with ischemic LV dysfunction ($EF \leq 35\%$) and severe CAD eligible for CABG were randomized to CABG + OMT or OMT alone. Patients with $\geq 50\%$ left main disease or class III-IV angina were excluded. There was no significant reduction in mortality at 5 years but a significant reduction in mortality in the extension study after 10 years (all-cause mortality 58.9% vs 66.1%, $p=0.02$, CV mortality 40.5% vs 49.3%, $p=0.006$). (29) There are some important limitations

to this trial, namely the crossover between groups and enrolment of patients without significant clinical HF (39% NYHA class I-II).

The viability substudy of STICH, looked at the outcome of 601 patients who, in a non-randomized fashion, underwent viability testing with SPECT, dobutamine stress echo, or both.(34) Viability was defined in a binary manner: 487 (81%) had viable myocardium. At a median follow-up of 5.1 years, there was no outcome difference in patients with viability according to the randomized treatment strategy (CABG+OMT vs OMT alone). The STICH viability study was limited by the non-randomized selection for viability testing, not using more advanced methods (CMR or PET), LV remodeling (mean LV end-diastolic volume index was severely dilated 123 mL/m²) and the observation that very few patients (19%) did not have viable myocardium.

The distinctions from PARR-2 and the STICH viability substudy may be explained by differences in patient selection, imaging modalities, and study methodology (**Table 1S Supplementary data**).

There are 2 other small RCTs. The HEART trial used stress echocardiography and randomized 138 patients with CAD and LVEF $\leq$ 35% to conservative therapy or angiography with the intention to revascularization and showed no outcome difference but was acknowledged to be underpowered.(21) Siebelink randomized 103 patients to FDG PET versus 99mTc-MIBI SPECT and showed no outcome difference.(23) Only 36 (35%) of the 103 patients had reduced EF $\leq$ 30%.(23) The small sample sizes of these studies precluded any definitive conclusions.

Imaging modalities to assess myocardial viability

The techniques for assessing myocardial viability are based on detecting one or more of the markers of dysfunctional myocardium; perfusion, cell metabolism, mitochondrial function, cell membrane integrity, contractile reserve, and scar (**Table 2**). All these modalities have advantages and disadvantages (**Table 2**). Respectively, all these methods can be used with good accuracy (**Figure 2S Supplementatry data**) when interpreted by acknowledged experts.

Dobutamine stress echocardiography (DSE) is used to assess regional myocardial contractile reserve.(35) Low-dose dobutamine can lead to increased contractility in dysfunctional segments that are viable. At higher doses, viable segments may further improve or show reductions in contraction, reflecting inducible ischemia, but will not show incremental contractility if they are scarred.(26,36,37) The reported sensitivity and specificity of DSE are 80% and 78% respectively in predicting regional LV function improvement following revascularization, considered the most specific of the methods in experienced hands (**3**)(**Figure 2S Supplementary data**). Intravenous contrast agents can be used to improve the

accuracy of DSE. Further, speckle tracking imaging represents a novel additional echo method to assess viability which can be used both at rest or with stress.(38,39)

Single-photon emission computed tomography (SPECT) is a widely available modality with well-established clinical and prognostic validation.(40) Radionuclide-labeled tracers sequester within myocytes with intact cell membranes and the regional concentration is compared to the peak uptake to assess viability. The most used tracers for viability imaging are the potassium analog thallium-201 (^{201}Tl) and lipophilic intramitochondrial molecule technetium-99m ($^{99\text{m}}\text{Tc}$) -labeled compounds, whereby their cardiac uptake reflects sarcolemma membrane integrity and mitochondrial function respectively.(3,41) Compared to techniques based on the assessment of residual contractile recovery, SPECT has higher sensitivity and lower specificity.(3)

Positron emission tomography (PET) imaging using perfusion tracers such as ^{13}N -labeled ammonia ($^{13}\text{NH}_3$) or Rubidium-82 (^{82}Rb) combined with images using the glucose analog 18F-fluorodeoxyglucose (FDG) is an effective technique to provide information on both myocardial perfusion and metabolism.(42-44) Concordant reduction in both perfusion and FDG uptake ("flow-metabolism match") indicates irreversibly injured scarred myocardium; whereas regions in which FDG uptake is increased relative to a perfusion defect ("flow-metabolism mismatch") represent myocardial hibernation (**Table 3**). Healthy myocardium also uses glucose in the non-fasting state. The preparation for FDG PET viability imaging is straightforward and involves 12 hours fast and then an oral glucose load, then monitoring the glucose level. Patients with abnormal glucose response, will receive insulin. In patients with known diabetes, the insulin clamp is the preferred approach as it yields the best quality images.(45) An example of a PET viability study is shown in **Figure 1**.

Cardiac Magnetic Resonance (CMR), combined with the use of gadolinium-chelated contrast agents, can provide information on perfusion and viability concomitantly. Gadolinium does not penetrate myocytes with intact membranes. The contrast agent has a greater volume of distribution into regions of altered cell permeability as occurs in scarred or acutely infarcted tissue, enabling the assessment of the transmural extent of necrosis and the presence of viable tissue. In conjunction with dobutamine stress, CMR can also provide information on global LV function, regional wall motion, and thickening.(47) Romero et al. pooled 24 CMR viability studies with 698 patients looking for functional improvement after revascularization. They found that delayed gadolinium enhancement $<50\%$ of wall thickness, $>2\text{mm}$ wall motion change in low-dose-dobutamine infusion and $>5.5\text{-}6\text{mm}$ end-diastolic wall thickness predicted functional myocardial recovery measured by serial CMR.(20) There is data supporting that even when the end-

diastolic wall thickness is $\leq 5.5\text{mm}$, there is potential for recovery as long as the scar is not transmural.(48) Dobutamine CMR can detect ischemia and viability by contractive reserve. Adenosine CMR can detect perfusion and define regions at risk of ischemia. Native T1 tissue mapping is an emerging method to assess transmural of infarction without contrast.(49) **Figure 2** illustrates an example of a CMR study.

Data regarding cost-effectiveness of viability testing and the different modalities is limited. One study applied a “decision analysis model” that evaluated patients undergoing revascularization or not and PET imaging or not; an algorithm was developed. They demonstrated that viability PET imaging “may be cost effective in the selection of patients with poor LV function referred for CABG”.(50)

The optimal choice of which modality to use is determined in part, by patient characteristics and local factors (expertise, availability and practice patterns). In the absence of direct comparative outcome evidence, the authors suggest the following approach (51,52):

- 1) Moderate LV dysfunction –any modality with local expertise.
- 2) Severe LV dysfunction –nuclear methods (SPECT, PET) or CMR LGE which are more sensitive than contractile reserve.(3,20)
- 3) Renal failure (GFR <30) or CMR incompatible devices –avoid CMR.
- 4) Critical left main or proximal 3-vessel disease –avoid dobutamine.
- 5) Equivocal or negative results on another viability test, where certainty is needed to completely rule (in or) out viability –consider PET or CMR as highly sensitive methods.(3,20)

Clinical perspective

The decision whether to revascularize a patient with significant left ventricular dysfunction can be one of the most difficult decisions in medical practice notably in patients without significant ischemia or angina. Since RCT data has not supported routine use of viability imaging in IHF, its use should be limited to situations where decisions are most difficult. Based on post-hoc analyses and observational data, viability imaging may contribute to risk stratification and selection of patients considered eligible for myocardial revascularization. (3,4,16,18-20,28,53)

GDMT includes: optimal pharmacological and non-pharmacological therapy for all patients and implantable device therapy for appropriately selected patients, as key therapies for IHF patients. The selection for percutaneous mitral valve procedures is still in evolution.(54,55) As well, left ventricular assist devices and cardiac transplantation are advanced treatment options for a minority of the patients. Revascularization offers the potential for improved survival and quality

of life for certain patients with IHF.(25,27,29,32,56) Post-hoc RCT and observational data suggest that this may be in particular for those with high ischemic burden and viable myocardium and/or low scar burden.(3,4,16,18-20,28,53,56) Other potentially useful parameters to guide therapeutic strategies include remodelling, LV ejection fraction, right ventricular failure, pulmonary hypertension, mitral or tricuspid regurgitation as well as duration of cardiac dysfunction as suggested by Bax et al. and others.(53,57) However the intersection and application of these complex parameters into a clinical decision remains a challenge.

Guideline-driven management supports revascularization for patients with IHF if they have reversible ischemia or a significant amount of viable myocardium above the method-specific cut-offs.(58)(**Table 4**)

Assessment should include scar burden (defined as the total amount of scar in the LV expressed as a percentage of the total LV) since it is an independent prognostic factor as well as an important variable for treatment choice.(20)(31) The degree of LV remodeling also plays an important role. It is known that advanced remodeling in IHF is associated with poor outcomes regardless of presence of viability/ischemia.(59-61) In at least one study, even viable myocardium did not improve with revascularization in the context of extensive remodelling.(62) On the other hand, others suggest that a larger LVESVI (>79ml/m²) actually favors revascularization.(63) Therefore, the data on the interaction of remodeling and viability extent is contradictory and currently, there are no validated remodeling cut-offs for revascularization benefit.(61-63)

Viability testing should be limited to patients with IHF where revascularization decisions are ambiguous and most difficult, such as in patients without angina nor demonstrated reversible ischemia with moderate to large regions of fixed perfusion defects, and/or with multiple co-morbidities (**Table 5**).

In some patients the decision to revascularize is less controversial and in this cohort, viability testing is unlikely to be of benefit.(51,63) These characteristics are: angina CCS > II, patients with normal or mild left ventricular dysfunction, critical left main CAD, patients with good revascularization targets, those with already demonstrated moderate to severe ischemia and those with minimal or no comorbidities.(52,63)

The assessment of myocardial viability with non-invasive imaging modalities may be of importance in certain cohorts such as patients with chronic total occlusions (CTO) before the decision of revascularization.(64)(65) **Table 5** lists important clinical and imaging variables that can aid in the decision for requesting viability testing for patients with HFrEF. This is based on the best current knowledge and evidence that unfortunately does not include high quality data achieved through very large well powered randomized controlled outcome trials. (51,63-65)

Several recently proposed algorithms could be adopted for viability testing in clinical practice.(52,66,67) The presence of ischemic symptoms may define patients who will derive *symptomatic* benefit from revascularization.(68,69) Patients who predominantly have HF symptoms, may benefit from viability testing if they have low-intermediate procedural risks without high-risk coronary anatomy features (**Figure 3**).

Contributing factors to clinical decision making

The total amount of myocardium in jeopardy (viable and/or ischemic myocardium) is intuitively pivotal regarding the benefit from revascularization, although most studies have addressed them separately and some shown contradictory results. In the analysis of Ling et al. for 648 patients with mean LVEF of 31% undergoing PET, the percentage of viability was prognostic for benefit from revascularization but ischemia and scar were not.(24) Further, in STICH, inducible ischemia with stress SPECT or dobutamine echocardiography, did not correlate with survival prognosis, similar to the findings from STICH-viability assessment discussed previously.(70) In a trial of 719 mostly non-HF patients (only 15% with HFrEF) the patients with moderate to high ischemia burden on stress SPECT had better long-term outcomes after undergoing timely revascularization compared to pharmacological therapy only.(71) Complementary findings were observed in a previous large cohort of 13555 mainly non-HF patients, optimal medical therapy was superior to revascularization in patients with minimal ischemia.(72) The ISCHEMIA trial which recently completed enrolment will shed further light on this concept, although not in patients with more severe LV dysfunction (Available from <https://clinicaltrials.gov>, NCT01471522).

The upfront risk of operative mortality is greater in patients with severe LV dysfunction and needs to be balanced with the possible long-term benefit. The utility of viability testing seems to be greatest in patients where both the risks and benefits of revascularization are the highest. A meta-analysis of 26 observational studies with 4119 patients (mean age 64 years, LVEF $\leq$ 35%) undergoing CABG showed an operative mortality of 5.4%.(73) Surgical mortality risk calculators such as Euro SCORE II (<http://www.euroscore.org/calc.html>) and the STS score (Society of Thoracic Surgeons) (<http://riskcalc.sts.org/STSTWebRiskCalc273/de.aspx>) should be used for guidance. In the STICH trial, the early increased risk with CABG and long-term benefit curves crossed at 2 years, and thereafter mortality was lower in the CABG subgroup.(22)

The arrhythmogenic potential of viable myocardium might play an important role. Studies have shown that the prognostic benefit of revascularization in patients with viability is not tied to improved LV function alone.(74,75) One mechanism for the mortality reduction is related to revascularization of myocardial regions with potential to cause lethal arrhythmias.(76,77) Sympathetic nerves are more sensitive to ischemia compared to the myocytes. The PARAPET study demonstrated that a greater amount of sympathetic denervation measured by 11C-HED-PET correlated with greater risk of sudden cardiac arrest.(78) In another study using voltage mapping it was demonstrated that hibernating myocardium displays abnormal and heterogeneous properties creating arrhythmogenic potential.(79)

Guidelines for Viability Imaging in Heart Failure

The current task force guidelines from CCS, ACCF/AHA and ESC offer only general recommendations regarding viability imaging. They state that imaging for myocardial viability (and ischemia) is reasonable in select situations in patients with HF considered suitable for revascularization (80) and that noninvasive imaging modalities might provide critical information needed,(81) although the limited experience from RCTs has not been able to demonstrate the routine benefit from viability testing.(58,68,80,81) For recent Heart Failure Guidelines, the class of recommendations for viability imaging is graded IIA (should be considered, level of evidence B-C) (80) or IIB (may be considered, level of evidence B) (68,81) largely because of the lack of support from large RCTs.

Ongoing trials and future directions

The results of the STICH viability study questioned the value of viability testing and has likely led to decreased utilization of viability imaging (or perhaps less inappropriate testing). The journey of viability testing is a fine example of constantly evolving knowledge translation and best practices of seemingly well-established concepts. It has become apparent that conducting a randomized study on the benefit of viability testing in guiding revascularization is challenging, as therapeutic decision-making is difficult to control. Without supporting data from the existing RCTs, it is clear that not all patients with HF and CAD require viability testing before revascularization decisions.(4,16,21-23,34) Specifically, viability imaging is not likely to add value in patients with already documented moderate-severe ischemia, angina or severe left main/proximal LAD disease as these parameters are generally enough for clinicians to make revascularization management decisions.(22,29,34,67,68,72,82) On the other hand there is a

growing number of patients with diffuse epicardial CAD, microvascular disease and/or significant comorbidities such as advanced age or diabetes. Based on post-hoc RCT data and observational data, viability imaging may have value in patients with IHF (3-5,16,18-20,28,53,56,57) but as with any diagnostic test, it should only be applied when it may impact management decisions. This may be the case in such higher risk cohorts but further research is needed in these populations to prove the potential benefit.

This field has evolved significantly over the past 20 years and future directions will explore personalized approaches to revascularization in HF including the role of CTO/complex anatomy, the method of revascularization, novel imaging techniques and serum biomarkers. The likelihood for improvement in symptoms and prognosis is multifactorial. It has recently been suggested that a comprehensive approach which considers clinical and imaging parameters, sometimes using multiple imaging modalities, provides complementary information that might improve prediction.(57)

The ongoing IMAGE-HF trial, AIMI-HF is a RCT and registry in patients with ischemic heart failure that compares standard care which includes SPECT imaging to define ischemia or viability to advanced imaging modalities using PET or CMR. This study may shed light on the impact of advanced viability imaging on clinical outcomes (composite of cardiac death, arrest, infarction and cardiac hospitalization) (Available from <http://clinicaltrials.gov> NCT01288560).

Further, beyond revascularization decisions, assessment of contractile reserve(83), defining regional scarring (84-86) and septal glucose metabolism (87) have shown potential in resynchronizing therapy (CRT) decision-making. Likewise contractile reserve, extent of scar, metabolism in the myocardium including the papillary muscles could in theory play a role in predicting response and aiding decision making for expanding catheter based valvular interventions (e.g. mitral clip procedures –although studies to date have not reported data on viability imaging).(54,55) Prospective studies are required to test these hypotheses.

Patients with Chronic Total Occlusion

While numerous registry studies have shown that successful revascularization of CTOs can be associated with favourable outcomes including improvement in LV function and mortality (88,89), more recent randomized controlled trials have been more sobering.(90-92) The use of viability or ischemia imaging in CTO trials has been limited. EuroCTO-trial had a requirement of a non-invasive imaging test to assess myocardial viability in the territory of the CTO if there was myocardial dysfunction.(90) Patients with angina or angina equivalent symptoms (n=396) without acute coronary syndrome were randomized for PCI+OMT vs OMT. The study demonstrated an improvement in symptoms and quality of life. In EXPLORE, patients with STEMI and concurrent CTOs were randomized to PCI of the CTO lesion early after primary PCI, or no PCI of the CTO

lesion. PCI to the CTO lesion did not result in higher LVEF. However, a subgroup analysis showed that if the CTO lesion was in the LAD, PCI to the CTO lesion was associated with significantly higher LVEF after 4 months. Baseline CMR was performed in 49% of patients. In dysfunctional segments with transmural extent of infarction <50% in the CTO territory, the CTO PCI resulted in significantly better recovery of wall thickening compared with no PCI.(91) However, the REVASC trial showed that PCI of CTO lesions did not improve either CMR assessed segmental or global LV function at 6 months but there was little room for improvement since baseline LVEF was >43% and 1/3 had no segmental wall motion abnormalities.(92)

While these trials used viability imaging as part of enrolment criteria, none of the trials were performed specifically in patients with significantly impaired LVEF with large territories subtended by a CTO and proven viability, whereby successful PCI may be expected to lead to a meaningful increase in LVEF. Indeed, the mean LVEF in EXPLORE was 41% in the PCI arm before randomization, and that of REVASC was >55%.

One potential utility of viability testing in the presence of a CTO is to enable appropriate clinical decisions on revascularization strategy for concurrent multivessel CAD. Collateral circulation assessed by angiogram is not an effective way to assess viability in CTOs (64,65,94) but viability imaging using thallium-201 SPECT, FDG-PET or CMR can accurately predict functional recovery after revascularization.(65,93-95) Prospective studies underway will assess whether viability/ischemia testing can detect which patients benefit from CTO PCI.(96)

Serum Biomarkers

High-sensitivity troponins and NT-pro-BNP have emerged as powerful prognostic markers in heart failure (97), with elevated levels seen in situations with myocardial supply-demand mismatch, increased myocyte turnover, myocardial apoptosis, wall stress and oxidative stress –similar processes to hibernation. In a pilot study of 49 patients with IHF, LVEF $\leq$ 45%, the presence and extent of viability assessed by FDG-PET correlated with hs-TnT and NT-pro-BNP levels independent of EF, age and eGFR as well as the presence of scar (98) raising the theoretical possibility to combine image-guided with biomarker-guided approach to assist decision making.(99) At present the evidence is limited.(100,101) The ongoing Bio-AIMI-HF substudy of the IMAGE-HF trial, noted above will help to answer whether these and other biomarkers with or without imaging can better predict which patients will benefit from revascularization.

Method of Revascularization

According to the current guidelines, CABG is recommended as the first revascularization strategy in patients with “LVEF $\leq$ 35%, multivessel disease and

acceptable surgical risk".(68) However, CABG vs. PCI randomized trials have excluded patients with severe HF. The ongoing REVIVED-BCIS2 will be the first randomized study on the impact of revascularisation with PCI on the outcome of patients with severe IHF and will also investigate viability specifically in segments amenable to revascularization.(102)

Novel Imaging Techniques

Novel hybrid/fusion imaging techniques; PET/CMR, PET/CT and stress-CMR will enable simultaneous assessment of different aspects of viability; metabolism, perfusion and anatomy. Sympathetic denervation imaging might also serve as a novel method of risk stratification and therapeutic target in IHF patients particularly around the prediction of risk for sudden cardiac death.(78)

Heart Team and Artificial Intelligence Approaches for Complex Decisions

The importance of a heart team combining expertise of heart failure, imaging, both surgical and interventional revascularization as well as anaesthesiologist and gerontologist cannot be over emphasized in making best decisions for these patients.(67,103,104) Ottawa-5 exemplified how the combined role of these experts with accessibility of technology could lead to outcome benefit.(28) In the future, machine learning/artificial intelligence may increase the diagnostic performance of any mode of (viability) imaging (105), which may be further integrated for complex clinical decision-making and a personalized approach to revascularization.

Summary

Definitive proof of whether viability imaging offers outcome benefit in HF patients has been elusive. It is likely that in the past, there was an over-reliance on viability information that was not needed to guide decisions in many patients. Currently decisions are made balancing patient related factors, risks of the intervention, anatomic data, functional data and the patients' perspective. Viability imaging should be limited to situations where revascularization decisions are most difficult. Physicians should consider viability imaging when imaging findings will impact decision-making. The results from ongoing trials and future evidence regarding the role in certain patient populations or clinical scenarios as well as the roles of biomarkers, neurohormonal imaging, and artificial intelligence will provide much needed evidence to optimize revascularization decision algorithms in this difficult patient population.

Short summary

Balancing procedural risks and possible benefit from revascularization is a key question in patients with heart failure of ischemic origin (IHF). Detecting viable but dysfunctional myocardium can aid in decision-making. Modern imaging techniques (PET, CMR, SPECT and stress echocardiography) demonstrate different aspects of viable myocardium. Viability testing should be limited to patients with IHF where revascularization decisions are ambiguous and most difficult, such as in patients without angina and ischemia, with multiple comorbidities or prior CABG.

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Figure legends

Figure 1

A) Rest N-13-ammonia perfusion (Rst, top row) and 18FDG metabolism (FDG, bottom row) PET viability study in a patient with documented multivessel disease to aid in revascularization decision-making.

Perfusion images demonstrate moderate to severe reduction in tracer uptake in the LAD territory and moderate reduction in uptake in the basal to mid inferolateral wall (RCA/LCX territory). The FDG images demonstrate an extensive area of mismatch in the mid to distal anterior wall and apex (white arrows).

B) Polar map with quantitative analysis of the scar amount (7%, match defect) on the bottom left and hibernating myocardium (22%, mismatch defect) on the bottom right. Given the significant amount of hibernating myocardium, coronary artery bypass grafting was recommended. From Wiefels et al.(46) with permission.

Figure 2

A) Cardiac magnetic resonance (CMR) images of a patient with a history of previous anterior myocardial infarction and occluded mid LAD on coronary angiogram showing subendocardial scar involving > 75% of the myocardium from the basal to apical anteroseptal wall, mid to apical anterior wall and apex, suggesting no viability in the LAD territory.

B) CMR images of a patient with occluded proximal LAD with collaterals, 95%

stenosis ostial LCX and occluded OM1 showing subendocardial scar from the basal to apical anterior wall, mid to apical anteroseptal wall, and basal to mid lateral wall involving < 50% myocardium, suggesting viability in the LAD and LCX territories. Given these findings, the patient underwent CABG. From Erthal et al.(52), with permission.

Figure 3. Proposed algorithm for the integration of ischemia/viability testing in guiding revascularization decisions in ischemic cardiomyopathy.

*Including Chronic Total Occlusions.

**>50% Left main/proximal LAD (left anterior descending coronary artery) stenosis.

***Ischemia/viability testing may be considered depending on patient, anatomy, targets and revascularization risk.

**** For eligible candidates.

EF= ejection fraction; CAD= coronary artery disease; (+) presence of, (-) absence of.

Adapted from Wiefels et al.(46) with permission. Based on Neumann et al.(68) and the clinical evidence from observational data and guidelines discussed in this paper.

Table 1. Definitions and cellular differences between normal and different types of viable dysfunctional myocardium.

Definition and picture	Structural / Phenotype	Metabolism	Cellular Membrane	Ca ²⁺ handling proteins	Others
Normal myocardium Preserved myocyte metabolism, cell membrane integrity, presence of blood perfusion, presence of contractile reserve and preserved wall thickness.	-Myofibrillar phosphorylation -Sarcomere in the perinuclear area	-Use of free fatty acids during fasting -Normal sarcoplasmic reticulum and O₂ consumption	-Adhesion molecules (β_1 integrin, N-cadherin, desmoplamin, vinculin) in the intercalated disc area at the distal area of cardiomyocytes	-Normal Ca²⁺ uptake -Normal levels of SERCA/2a	
Viable dysfunctional myocardium 	-↓ Myofibrillar volume density -↓ Protein (Actin, Myosin, Desmin, Titin) - Myocyte apoptosis	-Suppression of O₂ consumption -Suppression of mitochondrial function - ↑Glucose uptake (↑ GLUT1) - Glycogen deposit	-Redistribution of adhesion molecules to the lateral membrane increasing tensile force between cells	-↓Ca²⁺ influx -↓SERCA -↓SERCA2a	-↑Pro-inflammatory cytokines (TNF-α etc.) (9) -Upregulation of inducible nitric oxide synthase (iNOS) (9) -Sympathetic denervation -Changes in the expression of α- and β-adrenergic receptors

Remodelling:

Compensatory myocyte changes taking place in viable dysfunctional myocardium but also in remote normally perfused regions to maintain cardiac output. The changes in ventricular geometry, local wall strain, filling pressures and neurohormonal factors initially induce compensatory hypertrophy, but in long-term deleterious adverse remodelling and ventricular dilatation occurs (10,11).

Stunning:

Reversible contractile dysfunction after abrupt, transient ischemia (6). This situation normally occurs after a single brief episode of ischemia where, after prompt restoration of blood flow, the contractile dysfunction persists temporarily followed by recovery (which may be minutes, hours, days or weeks).

Hibernation:

Result from repetitive stunning, repeated episodes of ischemia, persistent perfusion defects at rest, or reductions in the coronary flow reserve (8,12,13). The contractile function at rest is reduced, what is thought to be a protective mechanism to down regulate oxygen consumption (and down-regulation of perfusion) to ensure myocyte survival (6,8,12). By definition, hibernating myocardium has the potential to recover with restoration of normal blood flow and therefore it can only be defined with certainty after revascularization. Serial histologic and proteomic studies post revascularization have shown that for the most part, the cellular changes are recoverable (7).

Adapted from (8,14). Pictures from (15), light microscopy pictures (on the left) and electron microscopy pictures (on the right), with permission.

Table 2. Imaging modalities to assess myocardial viability.

Modality	Mechanism	Findings indicative of viability	Advantages/disadvantages
Dobutamine echocardiography/ CMR	Contractile reserve*	Improvement by visual or strain rate imaging (echo)	A: Specific, widely available, without radiation, <i>can detect ischemia, assesses valvular disease</i> D: Interobserver variability, risk of dobutamine**
SPECT Thallium -201	Perfusion: Sarcolemma membrane integrity (K ⁺ analogue)	Tracer uptake: >50% of maximum	A: Widely available, moderate cost D: Radiation dose, moderate sensitivity with low specificity
Technetium -99m -labeled tracers	Mitochondrial membrane integrity	>50-65% of maximum	A: Widely available, moderate cost D: Moderate accuracy
PET Perfusion /metabolism	Perfusion: ¹³ NH ₃ , ⁸² Rb, ¹⁵ O-water Myocyte glucose utilization: FDG	Flow-metabolism mismatch = hibernation, (Match = non-viable)	A: Highly sensitive D: Limited availability, high cost, need for glucose load or insulin clamp in patients with diabetes
CMR	Late gadolinium enhancement (LGE) Wall thickness	Scarring (LGE) <50% wall thickness Systolic thickening of a dyskinetic segment	A: Highly sensitive, without radiation, assesses valvular disease D: Limited availability, high cost, risks in renal failure, cannot use with certain devices

- *Biphasic response; Dobutamine low-dose 5-10ug/kg/min leads to improved contractility in hibernating myocardium. Dobutamine high-dose up to 40ug/kg/min (+atropine) leads to increased oxygen consumption, induced ischemia and decreased contractility.
- ** Risk of potentially life-threatening complications 0.2% (37)
- CMR= Cardiac Magnetic Resonance; SPECT= Single-Photon Emission Computed Tomography; PET= Positron Emission Tomography; LGE= Late gadolinium enhancement.

Table 3. The patterns of viable and non-viable myocardium and their clinical relevance.

Myocardium	Flow/ Perfusion	Glucose metabolism (FDG)	Function/ Contractile reserve	Structural changes	Potential to recover/ Clinical relevance
Viable Stunning	Preserved (after transitory ischemic insult)	Variable (normal, increased or reduced)	Reduced	No	Likely to recover if ischemic injury does not persist or become repetitive; revascularization can prevent recurrent stunning
Hibernation	Reduced	Preserved or increased (=perfusion- metabolism mismatch)	Reduced	Yes some*	May have partial /delayed or full recovery if adequate revascularization can be achieved
Ischemia	Preserved at rest, impaired at stress	Normal at rest, increased at stress	Preserved at rest, impaired at stress	No	May benefit from revascularization to prevent recurrent ischemia
Non-viable Scar	Reduced	Reduced	Absent	Fibrosis	Unlikely to recover with or without revascularization

Adapted from (6,10,51) and data from multiple sources (3,4,5,16,24,28,46).
 Permission from Nihoyannaopoulos et al. (69) requested.
 FDG= 18F-fluorodeoxyglucose.* See Table 1.

Table 4. Findings on different imaging modalities for patients with ischemic LV dysfunction that indicate potential to improve LVEF after successful coronary revascularization.

Imaging modality	Findings
Dobutamine stress echo / stress CMR	Reversible ischemia or > 20% of the left ventricle shown as viable
Single-photon emission computed tomography (SPECT)	Reversible ischemia or a large segment of viable myocardium (> 30% of the left ventricle)
Positron emission tomography	Reversible ischemia or > 7-10% hibernating myocardium (or $\leq 27\%$ scar, assuming LV dysfunction due to IHD)
CMR LGE imaging	Less than 50% wall thickness scarring shown by LGE in ≥ 4 dysfunctional segments
Modified from authors Ezekowitz JA et al.,(58)(31).	

Table 5. Parameters for consideration when deciding which patients may benefit from viability assessment.

Viability testing is usually not needed and unlikely to add useful information		Viability testing may add useful information	
Younger patients		Older patients	
HFrEF with > class II angina		HFrEF without angina	
Proven moderate-severe ischemia on other testing		No evidence of ischemia; moderate to large persistent perfusion defects suggesting scar (but may be hibernating)	
Higher LVEF (> 40 %)		Lower LVEF (< 40 %)	
Left Main Coronary Artery Disease		Chronic total occlusion	
No or limited co-morbidities		Severe/multiple co-morbidities (renal insufficiency, COPD, prior CABG)	

HFrEF= heart failure with reduced ejection fraction; LVEF= left ventricular ejection fraction; CAD= Coronary Artery Disease; LVESVI= left ventricular end-systolic index; COPD= chronic obstructive pulmonary disease. Adapted from references (52,63,64,65).