Does Imaging-Guided Selection of Patients with Ischemic Heart Failure for High Risk Revascularization Improve Identification of Those with the Highest Clinical Benefit?

Imaging-Guided Selection of Patients With Ischemic Heart Failure for High-Risk Revascularization Improves Identification of Those With the Highest Clinical Benefit

Lisa M. Mielniczuk, MD, FRCPC; Rob S. Beanlands, MD, FRCPC

A 65-year-old man presented to his local emergency department with rapid atrial fibrillation and acute pulmonary edema. This patient had a history of hypertension, and 2 months before this presentation, he developed progressive exertional dyspnea. The patient deteriorated in the emergency department and went into cardiogenic shock. Emergent coronary angiography revealed diffuse 3-vessel disease: a 99% proximal left anterior descending coronary artery lesion, 90% mid-right coronary artery lesion, occluded large first marginal branch, and diffuse severe disease of the left circumflex coronary artery. The initial ejection fraction (EF) on echocardiography was 15%, with mild mitral regurgitation and an estimated pulmonary artery pressure of 55 mm Hg. The patient stabilized with an intraaortic balloon pump and intensive care unit management; however, because of the diffuse nature of the disease, he was not believed to be a surgical candidate. He was transferred to another tertiary-care facility for consideration of cardiac transplantation.

As part of this evaluation, a PET viability study was done that demonstrated a significant area of perfusion-metabolism mismatch in the entire anterolateral wall. Less than 1% of the myocardium was scar, and 28% was defined as hibernating (Figure 1).

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The results of the viability test were pivotal in the decision to perform coronary artery bypass graft (CABG) surgery in a patient who otherwise would not have had surgery. Approximately 2 months after his initial presentation, the patient had a 4-vessel CABG. His predischarge echocardiogram demonstrated an EF of 25%. Six months after surgery, the patient was clinically stable with New York Heart class II functional symptoms and an EF of 45%.

Introduction and Definitions

This patient had a significant amount of hibernating myocardium. Myocardial stunning and hibernation are clinically important causes of myocardial dysfunction because both conditions indicate viable myocardium. Viability refers to living myocardium, and when used in the context of dysfunctional myocardium, viability implies that the tissue is alive and that the dysfunction is potentially reversible. This is in contrast to scar, where the tissue is dead or necrotic and not recoverable. Myocardium that is supplied by a significant stenosis and thus subject to reversible stress-induced ischemia with subsequent restoration of flow and function is, by definition, viable. On the other hand, dysfunctional myocardium that is viable may also be remodeled tissue, stunned, or hibernating. Ischemia refers to the myocardial metabolic state that results from an imbalance of blood supply and demand, resulting in reversible dysfunction. Stunning refers to a state of left ventricular (LV) dysfunction that persists after an episode of ischemia and restoration of normal blood flow. The time of

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recovery depends on the duration, severity, and size of the ischemic insult.\textsuperscript{1,2} Repetitive stunning episodes may result in hibernation of tissue. Hibernation refers to the metabolic down-regulation in response to repetitive stunning or a persistent state of reduced myocardial perfusion. In contrast to the acute reversible tissue injury resulting from ischemia, hibernation is a more-persistent downregulated, but still reversible myocardial state.\textsuperscript{1,3–5}

Coronary artery disease is the most common substrate for the development of LV dysfunction and heart failure (HF).\textsuperscript{6} As such, the role of revascularization in these patients is an important consideration, but it is often tempered by concerns over risk and lack of perceived benefit.\textsuperscript{7–9}

Cardiac imaging is an integral component in the evaluation of the patient with ischemic cardiomyopathy. Standard imaging modalities can provide incremental information about ischemia as well as LV size and function, all of which have important prognostic information that assist with decision-making. However, in addition to these routine diagnostic methodologies, certain imaging approaches have the ability to differentiate between myocardial scar and viable myocardium or to define myocardial hibernation. This carries important prognostic information and can be used to select patients who are most likely to benefit from a strategy of revascularization.

Ischemia and viability testing have emerged as strategies to select patients who will benefit from coronary revascularization in the setting of LV dysfunction and are recommended approaches in multiple guidelines (Table 1).\textsuperscript{10–15} Noninvasive perfusion studies can identify ischemia, the magnitude of which relates to the risk of subsequent cardiac events\textsuperscript{16–21} and the likelihood of survival benefit from revascularization.\textsuperscript{20}

There remains some controversy over the precise role of viability testing in patients with ischemic HF; however, on careful analysis of the current evidence, it is clear that a selected approach to viability testing is indicated in the evaluation of these patients. In light of the Surgical Treatment for Ischemic Heart Failure (STICH) trial results,\textsuperscript{22} it becomes even more crucial to identify patients who are likely to benefit from a strategy of revascularization. Viability testing may not be beneficial in all patients and depends on the experience of the healthcare team, the type of test ordered, and the clinical interpretation of the data. However, an imaging-guided strategy in select patients at high-risk for revascularization will improve the identification of those with

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**Figure 1.** A rest rubidium 82 and $^{18}$F-fluorodeoxyglucose (FDG) PET viability imaging study in corresponding short-axis, horizontal long-axis, and vertical long-axis slices. Perfusion images demonstrate a moderate to severe reduction in perfusion defect in the entire anterior wall, anterolateral wall, and apex. The lateral wall also has a moderate to severe perfusion defect. The FDG images (second row) demonstrate FDG uptake in the anterior wall extending to the apex and lateral wall, corresponding to a total scar score of 0.54\% and a mismatch score of 26\% of the ventricular myocardium.
the highest clinical benefit. There is a wealth of evidence to indicate that imaging of hibernating viable myocardium can identify patients at highest risk who are more likely to benefit from revascularization in terms of EF, symptoms, quality of life, hospitalization, and cardiac death. Cost-effectiveness has also been observed, but data are limited.29

### Rationale for Ischemia and Viability Testing

LV function is one of the most powerful predictors of prognosis in the setting of HF or following a myocardial infarction. It is important to differentiate LV dysfunction caused by necrosis and scar tissue formation versus LV dysfunction because of ischemia or hibernating, but viable myocardium. Identification of the latter group of patients predicts substantial survival benefit, symptomatic improvement, and improved LV function with revascularization.19,20,30

Quantitative gated perfusion imaging has been demonstrated to have independent and incremental prognostic value over clinical risk in identifying patients at a greater risk of refractory HF.20,31 Although LVEF predicts outcome, it is the degree of ischemia on single-photon emission CT (SPECT) myocardial perfusion imaging that predicts the likelihood of survival benefit of revascularization over medical therapy.19,32 In addition to SPECT imaging, perfusion PET, cardiac magnetic resonance (CMR), and dobutamine stress echocardiography (DSE) can identify patients with a higher rate of major adverse cardiac events.19 LVEF reserve (stress–rest LVEF), stress EF obtained from gated SPECT, and PET imaging can provide independent and incremental value for predicting future adverse events.16–18

Thus, ischemia testing is an indispensable part of the evaluation of patients with ischemic cardiomyopathy.

In the presence of ischemia or known angina, revascularization decisions often are straightforward. The benefit of revascularization in these patients likely results from improved perfusion of myocardial territories in jeopardy, preventing cell death and ultimately adverse clinical events.19 The role for viability imaging to direct therapy in such patients is probably limited. In the absence of typical anginal symptoms, patients may present with dyspnea-induced anginal equivalents or simply with other signs and symptoms of HF. However, clinically significant ischemia or residual viability (when ischemia is not apparent on routine ischemia testing) may be found in this latter group of patients, the presence of which is associated with improved outcomes after revascularization.20,26,30,33,34

### Accuracy of Viability Testing

In discussing the relative merits of an imaging-guided strategy to refine risk and predict benefits from surgical revascularization, it is important to note that not all methods of viability assessment are equivalent. At present, head-to-head comparisons of one viability test to another have been limited, but relative strengths and potential weaknesses emerge from each test. Available data suggest that SPECT and especially PET are highly sensitive (sensitivity of PET, 85%–90%; sensitivity of SPECT, 70%–75%), with a higher negative predictive value than DSE.30 DSE has the advantage of availability and a higher specificity and positive predictive value than radionuclide methods.30,35,36 Cardiac PET using 18F-fluorodeoxyglucose is considered the most sensitive modality for detecting hibernating viable myocardium30 (Figure 2). Although the experience with contrast-enhanced MRI (CMR) is more limited, recent results suggest that it offers similar predictive accuracies as those seen with DSE.37–39 Scar can be easily detected using late gadolinium enhancement. The extent of
A landmark study, Kim et al.\textsuperscript{46} demonstrated an inverse correlation between the transmural extent of late gadolinium enhancement before revascularization and the likelihood of improvement in regional contractility 2 to 3 months postrevascularization (Table 2). A major advantage of CMR is the ability to integrate different information about anatomy, wall motion, myocardial perfusion, and tissue characterization in a single comprehensive examination.\textsuperscript{38} However, CMR is limited by both availability and applicability in this patient population, where a significant proportion may have implanted devices and renal failure. The predictive accuracies of these diagnostic tests are also influenced by the level of local expertise.\textsuperscript{33,47,48} However, outcome benefits can be achieved in centers with clinical expertise in the acquisition and interpretation of these data by imaging experts and use by experts in HF and revascularization.\textsuperscript{49} This needs to be considered in any interpretation of the literature supporting or refuting a benefit of viability testing in patients with HF.

Viability Testing Predicts Recovery of Ventricular Function

The presence of myocardial viability has been shown to be predictive of global and regional improvements in LV function. A systematic review by Schinkel and colleagues\textsuperscript{30} revealed that nuclear imaging techniques have a relatively high sensitivity, whereas DSE has the lowest sensitivity in the prediction of global improvement. This is in line with prediction of improvement in regional function where fluoro-oxideglucose PET is the most sensitive.

The definition of improved global function is relatively homogenous across studies, with an improvement of \( \geq 5\% \) considered significant. The proportion of patients with viable myocardium showing a significant improvement in LVEF is variable, ranging from 36\% to 88\%. This is partly explained by heterogeneity in the definition of viability used.\textsuperscript{30,50}

Some studies have indicated that the improvement in ventricular function in the setting of viable myocardium is associated with a more favorable clinical prognosis.\textsuperscript{51} However, it is not clear whether the LVEF has to improve significantly to derive benefit from revascularization. Data from a small retrospective cohort study suggested that failure to improve LVEF following revascularization did not result in significant differences in HF score or cardiac outcomes compared with patients whose EF improved by \( \geq 5\% \).\textsuperscript{52} These results suggest that there may be beneficial results to revascularization that extend beyond improvement in contractile function, possibly by the reduction of subsequent ischemic events.

Viability Testing Improves HF Symptoms

From a clinical perspective, it is relevant to predict improvement of HF symptoms or exercise capacity following revascularization. Di Carli and colleagues\textsuperscript{27} demonstrated in a small study that the magnitude of improvement in HF symptoms following revascularization was related to the preoperative extent and magnitude of improvement in HF symptoms following revascularization. When management adheres to PET recommendations for revascularization, there is also an associated improvement in quality of life.\textsuperscript{28} In a pooled analysis of the limited number of studies addressing this issue, patients with viable myocardium were observed to have an improvement in New York Heart Association functional class, whereas in those without viability, the functional class remained unchanged.\textsuperscript{53,54}

Viability Testing Is Cost-Effective

An economic model was developed to compare the cost-effectiveness of a PET-guided imaging strategy compared with revascularization in all patients or medical therapy in all patients. This hypothetical model demonstrated that a PET-guided strategy to select patients for surgery was cost-effective and that the prevalence of hibernation and the survival rate of patients refused revascularization on the basis of PET results were areas most likely to influence cost-effectiveness.\textsuperscript{29}

**Table 2. LGE CMR for Prediction of Myocardial Functional Recovery (per Segment Analysis)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. Patients</th>
<th>Mean LVEF, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al\textsuperscript{46}</td>
<td>2000</td>
<td>41</td>
<td>43</td>
<td>97</td>
<td>44</td>
</tr>
<tr>
<td>Lauerma et al\textsuperscript{41}</td>
<td>2000</td>
<td>10</td>
<td>44</td>
<td>62</td>
<td>96</td>
</tr>
<tr>
<td>Selvanayagam et al\textsuperscript{42}</td>
<td>2004</td>
<td>52</td>
<td>62</td>
<td>95</td>
<td>26</td>
</tr>
<tr>
<td>Wellhofer et al\textsuperscript{43}</td>
<td>2004</td>
<td>29</td>
<td>32</td>
<td>90</td>
<td>52</td>
</tr>
<tr>
<td>Gutterlet et al\textsuperscript{44}</td>
<td>2005</td>
<td>20</td>
<td>29</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>Beek et al\textsuperscript{45}</td>
<td>2009</td>
<td>37</td>
<td>38</td>
<td>70</td>
<td>65</td>
</tr>
</tbody>
</table>

Adapted from Bettencourt et al.\textsuperscript{38}

LGE indicates late gadolinium enhancement; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction.
Viability Testing Improves Patient Outcomes

Multiple nonrandomized studies have supported a role for viability testing in this patient population, using either nuclear or echocardiographic techniques. An early meta-analysis of 24 such studies documented a strong association between revascularization and improved clinical outcomes. There was no such benefit seen in the absence of viability. Meta-regression of pooled data in patients with viable myocardium demonstrated that as the severity of LV dysfunction increases, the potential benefit (reduction in risk of death and nonfatal events) associated with revascularization increases.33 A more recent meta-analysis by Inaba and colleagues26 confirmed earlier findings of a mortality benefit, with revascularization seen only in those with viability (Figure 3). In addition, based on different imaging techniques, these authors determined the amount of viable myocardium needed to lead to improved survival, which ranged from 22% to 44%. Fluorodeoxyglucose PET had the lowest amount of viability needed to predict survival benefit.

The PET and Recovery Following Revascularization 2 (PARR-2) randomized controlled trial enrolled 430 patients. Inclusion criteria were patients with an EF <35% and suspected or confirmed coronary artery disease who were being evaluated for revascularization, transplant, or HF management. PET-assisted decision-making compared with standard care showed a trend but did not reach statistical significance for the primary composite end point (cardiac death, myocardial infarction, or recurrent hospital admission for cardiac causes).55 However, some important additional observations are worth noting. The first is that a significant mortality benefit was observed in a predefined subset of higher-risk patients who had not undergone angiography. Second, post hoc analysis of the data investigating adherence to PET recommendations demonstrated that a significant reduction in adverse outcomes was evident when there was adherence to the imaging recommendations. Third, a statistically significant benefit of PET imaging was also demonstrated in centers with significant experience in imaging, HF, and high-risk revascularization.49 Finally, PARR-2 data emphasized that parameters such as EF and impaired renal function predict outcome regardless of whether there is revascularization. On the other hand, an important interaction between mismatch of perfusion and metabolism with revascularization exists such that as the extent of mismatch increases, so too does the likelihood of benefit from revascularization34 (Figure 4). Patients with a mismatch score ≥7% revascularization showed a decreased occurrence of the primary outcome (Figure 5). This is similar to the mismatch defect size defined in prior observational studies as identifying high-risk patients who would benefit from revascularization.4,5 This finding of the relationship between extent of hibernation and likelihood of recovery with revascularization is also consistent with prior studies. Hachamovitch et al32 demonstrated in >5000 patients that as the degree of ischemia increased, the likelihood of benefit from revascularization in-
creased. Shaw et al.57 demonstrated in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) Nuclear Substudy that the key to outcome benefits in this patient population was reduction in ischemia. Thus, information on hibernation and ischemia can be useful to assist the clinician in identifying patients who will likely benefit from revascularization versus medical therapy.

Viability Testing in the Post-STICH Era

Inherent to the discussion of viability testing in ischemic HF is the premise that revascularization is a beneficial strategy in patients with poor ventricular function. The STICH trial results do not negate the role of revascularization in these patients. This study randomized 1212 patients with an EF < 35% and coronary artery disease amenable to CABG to medical therapy alone or medical therapy plus CABG. There was no statistically significant difference in the primary end point of all-cause mortality. When the results were adjusted for multiple covariates, there was a benefit in favor of CABG. In addition, patients assigned to CABG had lower rates of death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes. Finally, one needs to consider the significant crossover rates between the study groups that may have diminished the benefits of CABG in the primary intention-to-treat analysis. In the study, 17% of the medical therapy group eventually underwent CABG, and 9% of the patients assigned to CABG never had bypass surgery. The most common reasons for crossover to CABG were progressive symptoms, acute decompensation, or family or physician decision. The as-treated analysis of this study showed a significant mortality benefit in favor of CABG.22 All these observations suggest that a role for revascularization exists in selected patients, and it remains possible that viability testing may be a modality to help in this selection.

The results of the viability substudy of STICH should not significantly temper the enthusiasm of such a strategy.58 Results from the STICH viability substudy suggest that identification of viable myocardium by SPECT or DSE do not add value in patient selection for surgical revascularization. Among the 1212 patients enrolled in STICH, 601 underwent assessment of myocardial viability, but this allocation was not randomized. Overall, mortality was lower in the group of patients who had viability, but this did not remain statistically significant after adjustment for other baseline covariates. In addition, the assessment of myocardial viability did not identify patients with a differential survival benefit from CABG compared with medical therapy alone.

The results of the STICH viability study need to be interpreted cautiously, especially in light of its limitations. The patient population was quite different from that reported in prior observational studies and in the PARR-2 randomized study, where the patients enrolled were those for whom the decision for revascularization was uncertain and, therefore, a potential need for a viability assessment.34 The patients in the STICH viability substudy had to have suitable coronary anatomy for revascularization and were already accepted for revascularization. In addition, they had less-comorbid disease, including frequently having single-vessel disease, infrequent previous CABG, low incidence of renal dysfunction, and low rates of HF. For such patients, it may be argued that viability imaging is not needed. In addition, viability testing was not randomized in STICH, which could have led to potential selection bias. Furthermore, only 19% of the patients were considered to have nonviable myocardium, which is far less than in most previous studies.47,55,56

The imaging protocols and analyses used in STICH were limited to DSE and SPECT. Neither more-sensitive viability imaging with PET nor accurate scar imaging with CMR were evaluated. Although DSE was used to assess hibernation through contractile reserve evaluation, SPECT imaging was primarily used to assess the presence or absence of tracer uptake, which does not consider ischemia or hibernation (Table 3). As already discussed, both are known to be critical in predicting outcome response to revascularization.32,34

Concluding Remarks

There is no doubt about the efficacy of ischemia assessment in selecting patients for revascularization. Myocardial viabil-
Patients With Heart Failure (Canadian Institute of Health Research) by the University of Ottawa. Current work by Drs Mielniczuk and team grant # CIF 99470).

Evidence supports the notion that when viability testing is done with validated protocols in experienced and capable centers, the demonstration of a significant amount of hibernating myocardium can predict the patient who will most likely benefit from a therapy. Viability assessment should be ordered in circumstances when it will affect decision-making, and results must be interpreted in light of the particular clinical setting. Viability testing may not offer additional prognostic information in isolation but, rather, in the context of symptoms; LV size and function; comorbidities; and the potential for symptom, quality-of-life, and outcome benefit with revascularization versus medical therapy. Viability assessment should be ordered in circumstances when it will affect decision-making, and results must be interpreted in light of the particular clinical setting. Viability testing will offer the most benefit in patients in whom decisions regarding revascularization are more difficult and uncertain. Evidence supports the notion that when viability testing is done with validated protocols in experienced and capable centers, the demonstration of a significant amount of hibernating myocardium can predict the patient who will most likely benefit from a strategy of revascularization.

**Table 3. Characteristics of STICH Viability Study Compared With PARR-2 Data**

<table>
<thead>
<tr>
<th>STICH16</th>
<th>PARR-214,35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>Accepted for revascularization</td>
</tr>
<tr>
<td>75% multivessel disease</td>
<td>90% multivessel disease among patients with angiography</td>
</tr>
<tr>
<td>25% single-vessel disease</td>
<td>34% renal disease</td>
</tr>
<tr>
<td>7.5% renal disease</td>
<td>19% prior CABG</td>
</tr>
<tr>
<td>Viability testing</td>
<td>SPECT or DE</td>
</tr>
<tr>
<td>81% viable</td>
<td>22% viable by mismatch cutoff</td>
</tr>
<tr>
<td>Assessed ischemia or hibernation</td>
<td>DE: Yes—hibernation</td>
</tr>
<tr>
<td>SPECT: No—relative uptake</td>
<td></td>
</tr>
</tbody>
</table>

STICH indicates Surgical Treatment for Ischemic Heart Failure; PARR-2, PET and Recovery Following Revascularization 2; CABG, coronary artery bypass graft; SPECT, single-photon emission CT; DE, dobutamine echocardiography; FDG, fluorodeoxyglucose.

**Disclosures**

Dr Beanlands is a consultant for Lantheus Medical Imaging and Jubilant DraxImage and receives or has received research funding from Lantheus Imaging, GE Healthcare, and MDS Nordion.

**References**


Imaging-guided selection of patients with ischemic heart failure (HF) for high-risk revascularization should only be pursued when results are reliable, will affect decision-making, and will improve clinical outcomes (versus proposed surrogate markers). The decision to test and the interpretation of ischemia and viability testing should always be patient centered. While arguing opposing sides for the purposes of this “Controversies in Cardiovascular Imaging” article, on these principles, Drs Mielniczuk and Beanlands and I agree. To paraphrase holy texts, it may be easier for a camel to go through the eye of a needle than to rely solely on myocardial imaging to decide whether a patient with ischemic HF should undergo revascularization. Beyond the complexity and challenges of maintaining patient-centeredness, patients with HF present along a bidirectional continuum of symptoms, ventricular function and remodeling, and associated risk intersecting with clinical management teams: the Ottawa-FIVE substudy of the PARR 2 trial. J Nucl Med. 2010;51:567–574.

Response to Mielniczuk and Beanlands

Eric J. Velazquez, MD

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