

Revascularization in Severe Left Ventricular Dysfunction: Does Myocardial Viability Even Matter?

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ABSTRACT: Left ventricular dysfunction is a powerful prognostic predictor in patients with coronary artery disease and increasing number of patients with CAD and ischemic left ventricular (LV) dysfunction is a major clinical problem. Congestive heart failure is a frequent complication which is associated with significant health care costs and two-third of cases have ischemic cardiomyopathy. In such patients, coronary revascularization can lead to symptomatic and prognostic improvement and reversal of LV remodeling which led to the concept of viable myocardium to select patients in whom recovery of LV function and improvement of prognosis will outweigh the risk of surgical revascularization. The aim of this review article is to understand the different modalities for assessing myocardial viability and clinical impact of revascularization in relation to the evidence of viability in patients with LV dysfunction.

KEYWORDS: left ventricular dysfunction, myocardial viability, revascularization

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Introduction

Coronary artery disease complicated by severe left ventricular (LV) dysfunction is associated with high morbidity and mortality with increased risk of sudden death, ventricular arrhythmias and worsening heart failure and the choice of optimal treatment strategy in such patients is often challenging. Ischemic left ventricular dysfunction may be caused by myocardial stunning or hibernation. Acute myocardial ischemia rapidly impairs contractile function which can persist for several hours but is eventually followed by full functional recovery which is called myocardial stunning.^{1,2} Hibernating myocardium is chronically dysfunctional tissue in patients with coronary artery disease related to poor coronary perfusion. One third of the segments demonstrate early recovery whereas two-third of the segments may take upto twelve months for recovery. In these patients with multi-vessel disease, increased LV volumes, coronary revascularization may lead to symptomatic and prognostic improvement and these clinical benefits are accompanied by evidence of reverse LV remodeling. However, prospective identification of patients with ischemic heart disease and heart failure who may benefit from high risk revascularization remains a clinical challenge. This lead to the concept of viable myocardium to distinguish between LV dysfunction caused by infarction and scar tissue formation versus LV dysfunction due to ischemic but viable myocardium which has important clinical implications.^{3,4}

Assessment of Viability

Several imaging techniques looking at myocardial viability were developed with the aim of selecting patients in whom recovery of LV function and improvement of prognosis would outweigh the risk of surgical revascularization. Dobutamine stress echocardiography is used to assess myocardial contractile reserve. Low dose dobutamine (5–10 mcg/kg/min) can lead to increased contractility in dysfunctional segments that are viable. At higher doses, wall motion in these viable segments may further improve or diminish reflecting inducible ischemia. The biphasic response is highly predictive of viable myocardium and improvement of function after revascularization.^{1,5} Myocardial contrast echocardiography produces myocardial opacification and facilitates the identification of LV borders compared with conventional echocardiography.⁶ A study by Shimoni et al considered microvascular integrity to be a significant determinant of maximal myocardial contrast intensity (MCI) in humans and proved that preservation of microvascular integrity and perfusion by intravenous myocardial contrast echocardiography (MCE) predicts recovery of dysfunctional ischemic myocardium.⁷ Another study by Korosoglou et al in 2004 compared the diagnostic accuracy of myocardial contrast echocardiography with low dose dobutamine stress echocardiography (DSE) and of combined technetium-99 sestamibi single-photon emission computed tomography and

fluorodeoxyglucose-18 positron emission tomography. It involved 41 patients with ischemic heart disease who underwent cardiac imaging and a control group of 25 patients. It showed that MCE had 86% sensitivity and specificity of 43% to predict recovery of myocardial function, nuclear imaging had 90% sensitivity and 44% specificity whereas low dose DSE had 83% sensitivity and 76% specificity.⁸ Single photon emission computed tomography (SPECT) is widely available modality with well established clinical and prognostic validation. Tracers normally used in SPECT are Thallium-201 and Technetium-99m. Initial acquisition soon after thallium-201 injection indicates delivery of tracer through blood flow and images acquired four to twenty four hours later are a marker of sarcolemmal integrity which reflects tissue viability.⁹

FDG-PET (Fluoro-deoxyglucose-Positron emission tomography) is another modality to assess viability. Interpretation of FDG images typically includes a comparison of myocardial perfusion to myocardial metabolism. Regions that show concordant reduction in both myocardial blood flow and FDG uptake are considered irreversibly injured whereas regions in which FDG uptake was relatively preserved or increased despite reduced myocardial perfusion is a mismatch pattern and represents hibernating myocardium and is associated with high likelihood of functional recovery after revascularization.¹⁰ Cardiac MRI is another helpful tool which provides information on global LV function, regional wall motion and thickening. Application of gadolinium contrast agents can be used to detect perfusion defects, microvascular obstruction and areas of scarred tissue or fibrosis. Sensitivity and specificity of the above mentioned non-invasive modalities to assess myocardial viability are compared^{1,11,12} in Figure 1.

Viability and Clinical Outcomes in Patients with Ischemic Left Ventricular Dysfunction

In the 1970s, randomized controlled trials of CABG versus medical therapy for chronic stable angina excluded patients with LV dysfunction. Major advances in surgical care and medical therapy render previous data obsolete for clinical decision making. Meta-analysis by Allman et al in 2002 reported on results of 24 non-randomized studies carried out between 1992–1999 including 3088 patients with LVEF <40%. It

demonstrated significant association between revascularization and improved survival rate in patients with LV dysfunction and viable myocardium (79.6% reduction in annual mortality rate was observed-Fig. 2) and no benefit was seen with revascularization in absence of viability.¹³ The magnitude of the potential reduction in mortality increased as the severity of LV dysfunction increased. Benefit of revascularization was independent of the technique used to assess viability. It demonstrated high mortality in patients treated medically with viable myocardium. However, it had limitations including observational bias, non-randomized study designs and lack of standardization of medical therapy. There have been significant advances in the medical management of heart failure in the past decade. More randomized trials were done recently evaluating the benefit of viability study guided management of ischemic cardiomyopathy.

Surgical Treatment for Ischemic Heart Failure (STICH) trial published in 2010 was a prospective randomized study testing the hypothesis that CABG improves survival in patients with ischemic LV dysfunction compared to aggressive medical therapy.¹⁴ It also assessed the interaction between myocardial viability and survival in randomized patients who were all eligible for medical therapy alone and also eligible for CABG. In this substudy, the hypothesis was tested that assessment of myocardial viability identifies patients with CAD and LV dysfunction that have the greatest survival benefit with CABG compared to medical therapy.^{14,15}

It enrolled 1212 patients with ischemic cardiomyopathy and LV function <35%. All randomized patients were eligible for viability testing with SPECT myocardial perfusion imaging or Dobutamine stress echocardiography. A 17 segment model was used for the SPECT myocardial perfusion imaging and patients were considered viable if ≥ 11 segments manifested viability based on relative tracer activity and 16 segment model was used for dobutamine stress echocardiography and was considered viable if ≥ 5 segments with dysfunction at rest and manifesting contractile reserve with Dobutamine. Out of 1212 patients, 618 patients underwent myocardial viability test, 487 patients were considered viable (243 patients: 49.9% underwent medical therapy and 244 patients: 50.1% underwent CABG), 114 patients were considered non-viable (60 patients:

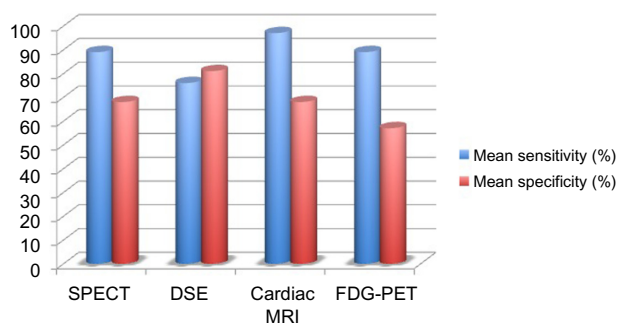


Figure 1. Non-Invasive Modalities to assess Myocardial Viability.

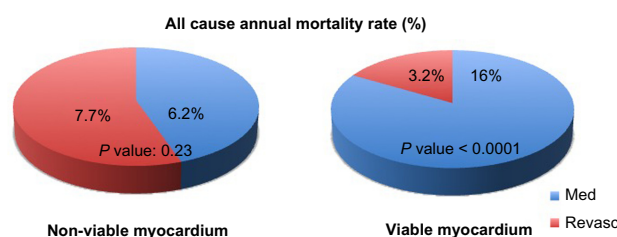


Figure 2. Annual mortality rate in patients with and without myocardial viability treated with revascularization vs medical therapy (Meta-analysis by Allman et al).

Abbreviations: Med, Medical; Revasc, Revascularization.



52.6% underwent medical therapy and 54 patients: 47.4% underwent CABG—Fig. 3). The trial failed to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to all cause mortality (P -value of 0.53— Fig. 4), thus signifying that in patients with CAD and LV dysfunction, assessment of myocardial viability does not identify the patients who will have greatest survival benefit from CABG versus medical therapy. However, there were some limitations of this trial. The patients selected for viability testing was solely based on physician's discretion. The viability testing was performed by two different imaging techniques and a standardized protocol with a single imaging technique was not used. Moreover, analysis was limited to SPECT and dobutamine stress echocardiography whereas cardiac MRI which is a gold standard technique for assessment of myocardial viability by late gadolinium enhancement was not used.

Prior to STICH study, PARR -2 (PET and Recovery Following Revascularization) trial in 2007 was done to assess the effectiveness of FDG-PET assisted management in patients with left ventricular dysfunction and suspected coronary artery disease which included 430 patients from nine centers between 2000–2004. Although, the event rate in the FDG-PET arm was less than the standard arm (36% in PET arm versus 30% reduction in standard arm, hazard ratio of 0.79), the overall study was inconclusive because there was no statistically significant difference for the primary outcome measure.¹⁶ Thus, it

did not demonstrate any significant difference in the reduction of cardiovascular events in FDG-PET assisted management versus standard care.

Revascularization Strategy: CABG vs. PCI

There is another dilemma in the management of patients with depressed ejection fraction, congestive heart failure and complex coronary anatomy who have limited treatment options. The majority of these patients may not be eligible for CABG as the surgical risk is often thought to be prohibitive. It raises the question: Does multi-vessel PCI give similar outcomes to CABG in patients with severe LV dysfunction?

Several head to head randomized controlled trials done over the past years have compared the outcomes of the two modalities in patients with multi-vessel CAD (BARI, ARTS, SYNTAX, FREEDOM). They demonstrated that PCI is non-inferior to CABG for the outcomes of death and major cardiovascular events. So far, only diabetic patients have shown a survival advantage with CABG over multi-vessel PCI, although BARI 2D trial showed no significant difference in the rates of death and major cardiovascular events between patients undergoing medical therapy versus prompt revascularization.¹⁷ Another meta-analysis of 19 studies involving 4766 patients was done by Kunadian et al in 2012 utilizing PCI among patients with LV dysfunction (EF <40%) to determine in-hospital and long term one year mortality. It demonstrated that PCI among patients with LV dysfunction is feasible with acceptable in-hospital and long term mortality and yield similar outcome to CABG.¹⁸ However, in all these studies, assessment of myocardial viability was not a prerequisite thus creating a dilemma as to which patient population (viable versus non-viable myocardium) actually benefited from any of the revascularization procedure in terms of mortality, major adverse cardiovascular and cerebrovascular events and quality of life.

BCIS-1 (Balloon pump-assisted coronary intervention study) was the first randomized controlled trial of elective intra-aortic balloon pump insertion prior to high risk PCI versus PCI with no planned IABP use. It enrolled 301 patients with impaired LV function (EF <30%) and extensive myocardium at risk with BCIS-1 jeopardy score of ≥ 8 or target vessel supplying occluded vessel which supplies $\geq 40\%$ of myocardium. It was found that in patients with severe ischemic cardiomyopathy treated with PCI and elective IABP use, 34% reduction was observed in long term all cause mortality.¹⁹

The PROTECT-II trial was the first prospective, multi-center study for patients requiring hemodynamic support during high risk PCI comparing outcomes between IABP and Impella 2.5. The Impella 2.5 device is a percutaneously placed left ventricular assist device that produces a non-pulsatile cardiac output of up to 2.5 L/minute. It included 447 patients out of which 223 underwent IABP and PCI and 224 patients underwent Impella guided PCI. Primary outcome was major

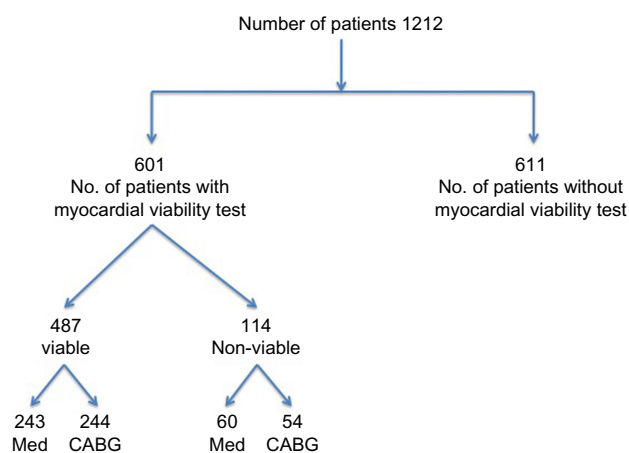


Figure 3. Patients Randomized in STICH Trial.

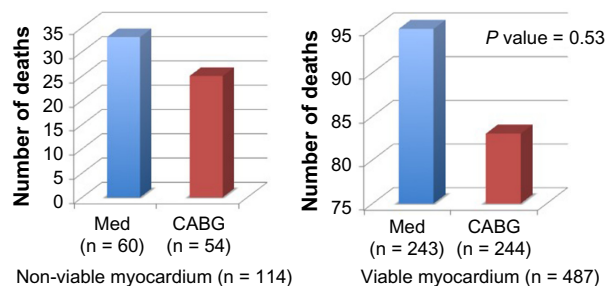


Figure 4. Myocardial Viability and Mortality (STICH Trial).

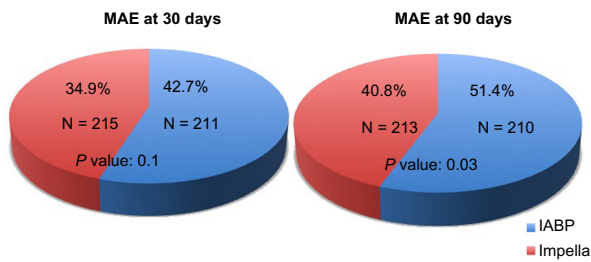


Figure 5. Major Adverse Events in patients with IABP vs Impella (Protect II Trial).

Abbreviation: MAE, Major adverse events.

adverse events (death, stroke, TIA, MI, repeat revascularization, acute renal dysfunction, increase in aortic insufficiency, severe hypotension, CPR or ventricular arrhythmia requiring cardioversion) at 30 days and 90 days. The study concluded that superior hemodynamic support of Impella appears to have led to significant procedural differences between the two arms and Impella arm had strong trends towards superior clinical outcomes for the entire intention-to-treat population with a significant reduction of major adverse events at 90 days follow up (Fig. 5).²⁰

Conclusions

Decisions about revascularization in patients with heart failure symptoms and left ventricular dysfunction are influenced by factors that do not always correlate with documented LV functional improvement. Lack of interaction between myocardial viability and benefit from revascularization in these studies suggest that assessment of myocardial viability might not be the sole deciding factor in selecting the best therapy for patients with left ventricular dysfunction due to coronary artery disease and medical management or multi-vessel PCI may also have similar outcomes to surgical revascularization. However, it is difficult to draw a definite conclusion according to the existing data and more randomized studies will be needed in this sector, grouping patients to three treatment arms including optimal medical therapy versus multi-vessel PCI versus CABG with blinded assessment of myocardial viability by cardiac MRI in all patients.

Abbreviations

- LV: left ventricle
- EF: ejection fraction
- CAD: coronary artery disease
- PCI: percutaneous coronary intervention
- CABG: coronary artery bypass grafting
- MCE: myocardial contrast echocardiography
- DSE: dobutamine stress echocardiography
- SPECT: single photon emission computed tomography
- FDG-PET: fluoro-deoxyglucose-positron emission tomography
- MRI: magnetic resonance imaging

IABP: intra-aortic balloon pump
CPR: cardiopulmonary resuscitation

Author Contributions

Conceived the concepts: PS, HK. Analyzed the data: PS, NS, NK. Wrote the first draft of the manuscript: PS. Contributed to the writing of the manuscript: PS, NK. Jointly developed the structure and arguments for the paper: PS, HK, NS. Made critical revisions and approved final version: PS, HK. All authors reviewed and approved of the final manuscript.

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