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Viability Study before Myocardial Revascularization in Current Era: A Viable Strategy

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Abstract

Last few decades have seen tremendous increase in patients with ischemic heart disease and despite advances in medical treatment patients with severe LV dysfunction are on rise due to improved survival rates. The myocardial revascularization has been attempted to aim at improving myocardial function and thereby symptomatic as well as survival benefit. LV dysfunction may be due to myocardial stunning and hibernation which are reversible causes of LV dysfunction and viability testing helps in differentiating them from necrosed myocardium as revascularization in patients with nonviable myocardium has no benefit but may be harmful.

Keywords: Viability; Revascularization; Pet; Spect; Cmr; Dobutamine.

With rising incidence and prevalence the ischemic heart disease has topped the list of leading causes of death globally even in developing countries like India and cardiovascular diseases (CVD) have emerged as the leading cause of death. Resultant left ventricular dysfunction (LVD) is important cause of morbidity with impaired quality of life and increased burden on social and financial services of the society. With left ventricle (LV) dysfunction proven to be an independent predictor of survival, strategies have evolved to improve LVD by various invasive and non invasive means including lifestyle changes, dietary modifications, physical activity, identification and treatment of risk factors, pharmacological treatment aimed at improving myocardial remodeling using drugs like angiotensin convertase enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBS), B-blockers, Aldosterone antagonists and myocardial revascularization by coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG). New concepts like stunning and hibernation have changed the way we look at infarcted myocardium and have changed the belief that LV dysfunction post myocardial infarction is irreversible. European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) recommend routine testing to assess myocardial viability before revascularization and advises to refrain from intervention in patients with no evidence of viability [1]. The risk–benefit ratio for revascularization in patients without angina/ischaemia or viable myocardium was always in a doubt and has never conclusively favored revascularization strategy. According to European guidelines Myocardial revascularization is preferred strategy in the presence of viable myocardium (IIa level B indication) [2]. Exercise testing and various cardiac imaging modalities as discussed below are non-invasive techniques to assess for myocardial viability before revascularization in patients with poor LV function. PET scan, SPECT scan, MRI and dobutamine stress echocardiography have been in use for assessment of viability and to guide decision making in myocardial revascularization of patients with chronic ischaemic systolic LV dysfunction [3]. The nuclear imaging have a high sensitivity but lower specificity in comparison to tests assessing myocardial contractility and reserve which have lower sensitivity but higher specificity. MRI has ability to assess anatomical as well as functional aspects with a high diagnostic accuracy for assessing the transmural extent of infarcted myocardium and ability to assess contractile reserve. The evidence to select between the various imaging modalities is coming from observational data as well as from metanalysis and availability remains the major factor

in determining selection of imaging technique.

PET scan- In one of the randomized controlled studies Beanlands and colleagues found that patients with significant LV dysfunction but viable myocardium on F-18-fluorodeoxyglucose positron emission tomography imaging are likely to benefit from myocardial revascularization [4]. In their observational study using FDG-PET in patients with severe LV dysfunction the investigators noted that benefit of early revascularization was more evident when percentage of viable myocardium exceeded 10% [5]. The viability sub study of the STICH trial 19% of patients had no viable myocardium [5]. It is noteworthy to note there was a statistically significant better outcome after revascularization in patients with viable myocardium on univariate analysis. Though the association was insignificant on multivariable analysis after inclusion of various prognostic variables the STICH sub study clearly and strongly gives message that if there is no viable myocardium revascularization would do more harm and no benefit. Similarly Hochman & colleagues found no additional benefit of revascularization over optimum medical treatment in asymptomatic/ stable patients post myocardial infarction [6]. Opening of chronically occluded vessels is not beneficial in the absence of symptoms or objective evidence of viability in the region supplied by the occluded vessel. Myocardial viability assessment of the region supplied by the narrowed/occluded coronary artery should be considered prior to intervention in patients with LV dysfunction [3]. Non viability indicates irreversible myocardial damage whereas viability denoted salvageable myocardium with potential benefit after revascularization. Revascularization in patients with irreversible damage only increases the risk of complications including death. Allan KC and colleagues in their meta analysis found that 35% of CABG or PTCA patients had benefit despite revascularization due to permanent myocardial injury i.e.non viability[3]. In their meta-analysis of 3088 patients with ischaemia heart disease mortality was almost 4 times lower after revascularization (CABG) in patients with dysfunctional but viable myocardium compared to pharmacological treatment alone. There was no significant difference between the efficacy of pharmacological and surgical treatments in patients with non viable myocardium on imaging. P Bax JJ et al showed improvement in myocardial dysfunction after revascularization suggestive of reversible injury in 25-40% of patients with LV dysfunction after myocardial infacrtion [7].

Spect-Based Viability Assessment

Single-photon emission computed tomography (SPECT) is a validated imaging investigation available with good clinical and prognostication data. It uses radionuclide tracers thallium-201 and technetium-99m (99mTc) –labeled compounds. Thallium being potassium analogue its uptake by myocardium is dependent on integrity of sarcolemmal membrane of heart muscle and regional blood flow.

The initial images denote the regional blood flow whereas late images reflect myocardial viability. 99mTc-labeled molecules have less redistribution with time; emit higher-energy photons with less attenuation and shorter half life compared to thallium. Gated SPECT has ability to assess regional and global myocardial function as well as viability. SPECT has higher specificity as compared to dobutamine stress echo.

Pet-based Viability Assessment

Fluorodeoxyglucose PET (FDG-PET) is "gold standard" in myocardial viability assessment. (F-18-labelled) glucose gets accumulated in the dysfunctional but viable myocardium and signifies greater probability of improvement in LV dysfunction after revascularization. The myocardium function may be acutely depressed due to stunning or may be hibernating due to prolonged critical ischaemia. On the PET scan stunned myocardium has normal or increased FDG accumulation indicative of adequate perfusion to viable dysfunctional myocardium. Reduced perfusion with normal or increased FDG accumulation indicates a hibernating myocardium [8]. Despite being gold standard standard PET imaging is not widely available, is costly procedure are is a costly procedure and has lower spatial resolution compared to MRI counterpart with gadolinium. The MRI is having almost 95% compatibility with PET scan, is more widely available, radiation free and gives anatomic as well as functional assessment [9].

Cmr-based Viability Assessment

The anatomical and pathological assessment in the form of infarct location, size, and extent of transmural infarction with extent of delayed enhancement using gadolinium on CMR is morphologically identical to the extent of necrosis observed on tetrazolium-based histopathological study [10].

MRI has better spatial resolution than PET or SPECT with detection of micro infarcts (less than 1gm

mass) and extent of thickness of infarcted myocardium and extent of delayed enhancement after gadolinium are used to assess viability and predict functional improvement after myocardial revascularization [11,12]. The late gadolinium enhancement (LGE) occurs due to accumulation of gadolinium in the extracellular space including vessels but no accumulation within the infarcted cells localizing the location of infarcted myocardium and assessing extent of infarction size.

In the study by Kim et al using cardiac MRI the extent of transmural infarction predicted the recovery 80% of segments with ≤25% transmural infarction scar improved function significantly after revascularization. In comparison less than 10% segments recovered when extent of transmural infarction was more than 50% [13]. Anatomically infarcted myocardium with thickness less than 5 mm predicts poor functional recovery. In addition to gadolinium the use of low-dose dobutamine can be used during CMR to assess for the viability and the probability of functional recovery. Thus, substantial hibernating or stunning myocardium can be detected, quantified and functional assessment can be done by CMR and these patients can benefit from revascularization.

Echocardiogrphy

Dobutamine stress echo- Echocardiography is commonly used for assessing myocardial contractility and contractility reserve. Pharmacological agents commonly used for stress echo are dobutamine and dipyridamole. 2D echo stress testing has advantage of wide availability, portability, less costly as well as familiarity with the drug. Low-dose dobutamine echocardiography can be used in patients with recent acute myocardial infarction. It is bedside technique, widely available, has a diagnostic accuracy of about 80% comparable to PET/SPECT scan, and easy to perform and safe after 24 hours after myocardial infarction in asymptomatic patients. Dobutamine is an ionotropic agent with biphasic response of improved contractility at lower dosages (5-10ug/kg/min) and abnormal wall motion at higher dosages if myocardium is viable. Dipyridamole acts by vasodilatation of coronary arteries increasing coronary flow leading to improved contractility in viable myocardium. Dysfunctional myocardial segments less than 5mm in thickness are suggestive of scarred myocardium and do not show improvement in contractility with any dose and hence unsuitablefor myocardial revascularization. The sensitivity and specificity of dobutamine stress echo is 84% and 81% respectively. However it important to note that stress echo is subjective with significant interobserver variability, has lower spatial resolution and diagnostic accuracy gets reduced in patients with poor acoustic window or severe LV dysfunction. Studies have shown that revascularization was beneficial in patients with stress echo suggestive of viable myocardium in comparison to pharmacological treatment alone.

Myocardial contrast echo- Microvascular integrity is an important pre-requisite for the viability in the dysfunctional segments. The microvascular integrity can be assessed using contrast echocardiography. Peak contrast intensity denotes capillary blood volume and correlates well with the microvascular density and capillary area, and is inversely proportional to the collagen content [14]. Contrast defect size assessed 10–15s after contrast administration correlates with the infarct size. The assessment of extent of transmural infarction by contrast echo correlates well with that predicted by CMR using late gadolinium enhancement. Thus myocardial contrast echo can be used reliably to predict functional recovery after revascularisation [15]. Because contractile response with dobutamine depends on microvascular integrity as well as myocardial blood flow dobutamine stress

Resting image	<5mm thickness / bright segments	Scar (non viable)
Low-dose dobutamine	5 to 10 mcg/kg/min infusion	
High-dose dobutamine infusion	up to 40 mcg/kg/min	(with addition of atropine)
Viability means (so as to benefit from revascularization)	contractile reserve- improvement of contractile dysfunction	at least ≥5 segments showing improvement during low-dose dobutamine infusion
Various responses		
(A) biphasic response (classical for viability)	Initial improvement on low dose followed by worsening of wall motion on high dose	represents viability with superimposed ischemia
(B) immediate worsening	Direct worsening of wall motion abnormality without any improvement	represents severe ischemia due to critical stenosis (viable)
(C) sustained improvement	Improvement of wall motion with no worsening	Denotes subendocardial infarction – (viable)
(D) no change	no change in wall motion at any stage	Scarred tissue (non viable)
CONTRAST ECHO	Homogenous uptake	Viable myocardium

echocardiography may be less sensitive than MCE for the detection of hibernating myocardium and MCE may be used to assess myocardial viability in patients having no significant response on dobutamine stress echo. MCE has superior sensitivity and comparable specificity compared with dobutamine echocardiography and superior specificity and comparable sensitivity compared to SPECT for the assessment of hibernating myocardium. MCE is useful bedside modality for the prediction of myocardial viability and independent predictor of post revascularization functional recovery [16].

Technique	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PET Scan (FDG)	92	63	74	87
SPECT scan Thallium 201	87	54	67	79
SPECT scan TC99	83	65	74	76
Dobutamine Stress echo	80	78	75	83
MRI wall thickness	95	41	56	92
MRI dobutamine	74	82	78	78
MRI Contrast enhancement	84	63	72	78

Table showing sensitivity and specificity of different imaging to assess viability before revascularization [18]

CT FFR-CT coronary angiography is highly sensitive to detect coronary artery disease but lacks specificity and has high false positive rate when compared to percutaneous coronary angiography. It is now well known fact that FFR guided PCI is beneficial in improving survival and optimizing results as shown in FAME and DEFER trials. Recent data has shown that FFR calculation during CT coronary angiography is feasible, non invasive and accurate in predicting hemodynamic significance of coronary lesions. FFR CT by combining anatomic and functional details has great potential to differentiate individuals who will benefit from revascularization with negative predictive value 93% and further larger prospective randomized studies are required before its routine use [17]. The FFR CT software is already cleared by FDA.

Stitch Trial-Surgical Treatment of Ischemic Heart Failure (STICH) trial was the first prospective randomized trial which tested the hypothesis that coronary artery bypass grafting (CABG) improves survival in patients with significant LV dysfunction when compared to aggressive medical treatment. The viability sub study of STITCH trial analyzed 601 patients. The tests used to determine viability was SPECT scan or Dobutamine stress echo. The protocol used for SPECT was 17 segment model with ≥11 segments should be having viability based on relative tracer activity whereas in *Dobutamine echo* 16 segment model was used with viable myocardium defined as ≥5 segments with dysfunction at rest manifesting contractile reserve with dobutamine infusion. Primary end point was all cause mortality whereas secondary end point was mortality or hospitalization. After follow up for 5 years post CABG the mortality in patients without viable myocardium was 50% whereas mortality was 33% in patients with viable myocardium. Though this association was rendered non-significant when subjected to a multivariable analysis that included other prognostic variables this study conclusively proved that optimum medical management alone rather than revascularization should be preferred in patients with severe LV dysfunction without significant viable myocardium.

Conclusion

Thus, percentage of viable myocardium is of clinical and prognostic significance. Myocardial viability should be routinely assessed by available best non invasive techniques to decide between revascularization and optimum medical treatment. Patients with significant LV dysfunction but large viable myocardium will improve drastically after revascularization. Nuclear scans like PET and SPECT, Stress echocardiography and MRI are non invasive modalities to assess myocardial perfusion and viability. Angioplasty or CABG results in higher mortality in the absence of viable myocardium y and optimum medical management should be default strategy in these patients deferring revascularization. With recent studies showing no survival benefit in multivariate analysis after revascularization despite having viable myocardium we need further large studies to understand impact of other factors in addition to viability and deciding best and appropriate line of treatment in this subset.

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