Assessment of Myocardial Viability: A Review of Current Non Invasive Imaging Techniques

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Introduction

Coronary artery disease (CAD) is the most prevalent and single most common cause of morbidity and mortality with the resulting left ventricular dysfunction (LVD) an important complication. Worldwide, CAD accounts for 5.7 million new cases per year, of these 1.3 million in Europe alone. In addition, it imposes a substantial share of health service resources and expenses, an impaired quality of life, disability and high social cost. Furthermore, LVD itself has been shown to be a powerful determinant of survival.

The once previously held notion that LVD in patients with CAD is always irreversible has been discounted. Indeed, the damaged myocardium can be at a state of stunning, defined as a prolonged contractile dysfunction after a transient acute ischemic insult and coronary reperfusion. Myocardial hibernation, reduced segmental myocardial function at rest and with stress, due to persistently impaired coronary blood flow, has also been shown to recover partially or completely after revascularization. In view of the evidence for potentially healthy myocardium, a myriad of invasive and non-invasive diagnostic techniques have been developed for the identification of myocardial viability. Indeed, the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) recommend the detection of myocardial viability a part of the diagnostic work up for revascularisation, and patients with no evidence for viability should be discouraged from procedures.

This review focuses on the scientific analysis of the existing evidence on the accuracy of the available diagnostic techniques including echocardiography, single-photon emission computed tomography (SPECT), positron emission tomography (PET), and cardiac magnetic resonance imaging (cardiac MRI) in determining the presence of myocardial viability.

Stress Echocardiography

Introduction

Echocardiography has been routinely used in the assessment of myocardial viability. There are four techniques employed; dobutamine stress, myocardial contrast, 2D gray scale wall motion scoring, tissue Doppler and more recently adenosine speckle tracking based myocardial strain imaging. Resting echocardiography highlights diastolic wall thickness of at least 5 mm as a marker of viable myocardium.

The most commonly used criterion to identify viable myocardium is by detection of contractile reserve. This is achieved by stress echocardiography using Dobutamine, Adenosine or Dipyridamole. An infusion of low-dose dobutamine (5–10 mg/kg/min) is administered which results in increased contractile function of viable segments whereas nonviable ones do not show such response. Myocardial viability can also be detected by using the biphasic response, with enhanced activity at low dose dobutamine and reduced function (ischaemia) at high dose dobutamine.

Using intravenous micro-bubble contrast, contrast echocardiography is able to demonstrate viability qualitatively. These micro-bubbles are inert gases and stay in the vascular space and behave like red blood cells in terms of rheology. Segments that have normal or patchy perfusion are classified as being viable in contrast to those with no perfusion who are taken as non-viable.

Doppler echocardiography uses optimum increase in coronary flow reserve (CFR) as an additional marker of viability. The underlying mechanism behind that is the increased myocardial metabolic demand with stress, which causes dilatation of the coronary vessels.

Additional information on myocardial viability can be obtained from adenosine speckle tracking based myocardial strain imaging. Usually at rest, there is no significant difference between the viable and nonviable myocardium strain. With adenosine stress, viable segments increase their longitudinal strain in contrast to non-viable ones which remain unchanged.

Low Dose Dobutamine Stress Echocardiography (LDDE)

The most recent meta-analysis by Schinkel AF et al (2007), of 33 studies (1121 patients); showed that low-dose dobutamine echocardiography had a cumulative sensitivity and specificity of 81% and 78% respectively, with a positive predictive value (PPV) and negative predictive value (NPV) of 75% and 83% respectively, (P < 0.05). It also found that high-dose dobutamine echocardiography had a higher sensitivity (83%) and NPV (85%) than low-dose dose (P < 0.05), whereas specificity and PPV were comparable [11]. A review by Camici et al (2008) examined 20 studies for myocardial viability in patients with LV dysfunction (LVEF ≤45%), and predicted functional recovery after revascularization; having shown that LDDE has superior specificity, lower PPV and similar NPV compared to nuclear imaging.

Myocardial Contrast Echocardiography (MCE)

Senior et al (2009) illustrated the accuracy of MCE for the prediction of myocardial viability, demonstrating a mean sensitivity of 85% and specificity of 70% [12]. Also, in the setting of ST-elevation myocardial infarction (STEMI) a review (2008) showed that MCE had a high sensitivity for predicting functional recovery after revascularization, but equivalent specificity compared with DSE. Finally, MSE and cardiac MRI have been shown comparable in predicting functional recovery.

Doppler CFR echocardiography

A study by Djordjevic-Dikic et al (2011) evaluated basal CFR and measured diastolic deceleration time (DDT) before elective
angioplasty in patients with prior MI, and demonstrated that the two measurements can predict myocardial function recovery. In a trial format Meimoun et al (2010) examined the prognostic value of CFR in predicting LV remodelling in acute MI in comparison to clinical, biochemical, electrocardiogram, and angiographic parameters, and concluded that CFR is an independent predictor of LV remodelling. It has been shown that patients with preserved CFR had better improvement in LV EF, and wall motion score and a fall in LV end diastolic volume compared to those with reduced CFR at 6-month follow-up.  

2D speckle tracking stress echocardiography; Ran et al (2012), in a recent trial assessed patients who had sustained a MI and EF of 40% (±6%) and showed that using adenosine stress, radial myocardial strain more than 9.5% had a sensitivity of 83.9% and a specificity of 81.4% for detecting viable myocardium, whereas a change of longitudinal strain more than 14.6% displayed a sensitivity of 86.7% and a specificity of 90.2%. Peak-systolic circumferential strain however, had little effect on viability assessment.  

Limitation and advantages  
The main limitations of echocardiography include; operator dependence, both in data acquisition, and interpretation, however, this could easily be overcome by good training and experience. Adequate acoustic window acquisition is another potential limitation but has greatly improved by using contrast agents. The main advantages of stress echocardiography include; good validity, wide availability, cost effectiveness, lack of ionizing radiation, and being friendly with implanted devices.

Prognostic value  
The VIAMI-trial (2012), was the first randomized control trial investigating a viability-guided invasive approach in 261 patients recruited at least 48 hours after an acute MI who then underwent LDDE for the detection of viability within 72 hours of MI. Those with a viable myocardium were randomized to an invasive or conservative treatment. The primary endpoint was the composite of death from any cause, recurrent MI and unstable angina at 1-year follow-up. An invasive approach in patients with a high viability score had a substantial reduction in ischemic events. The VIAMI-trial supports the concept that viability determines prognosis.

Single-Photon Emission Computed Tomography  
Introduction  
One of the most popular non-invasive nuclear imaging modalities used, is Single-Photon Emission Computed Tomography (SPECT). The main technique involve the administration of a radioactive tracer such as thallium-201 or Technetium Tc-99m, with Tc-99m sestamibi being the most widely used in clinical practice. The most commonly used criterion to identify viable myocardium is the percentage tracer uptake by the dysfunctional segments, where a tracer activity of >50% and redistribution of >10% are used as markers of viability as a consequence of preserved membrane integrity (detected by thallium SPECT). A tracer activity of >50% and improvement in tracer uptake after nitrates administration is also taken as a markers of viability, as a consequence of preserved mitochondrial function (detected by technetium SPECT).  

Various protocols have been developed to optimise the information obtained from thallium-201 imaging such as; stress-redistribution imaging, late redistribution imaging, thallium-201 re-injection and rest-redistribution imaging.  

Rest-redistribution imaging protocol  
Rizzello V. et al (2005) analysis of 22 studies (557 patients) using TI-201 rest-redistribution showed an average sensitivity and specificity of 88% (range 44-100%) and 59% (range 22-92%) respectively, and PPV 69% and NPV of 80%, for predicting regional function recovery; confirming previous meta-analysis by Bax et al (1997) of 8 studies, which showed a mean sensitivity of 90% and specificity of 54%. Similar results have recently been confirmed by Camici et al (2008).  

Thallium-201 re-injection protocol  
Re-injection protocol is an extra value on top of rest-redistribution results. Rizzello V. et al (2005) found lower specificity of 50% having analysed 11 studies (301 patients) and sensitivity of 86%, with low PPV of 57% and NPV of 83% [19]. Similar results were demonstrated earlier by Bax et al (1997), based on meta-analysis of 7 studies where an average sensitivity and specificity of 86% and 47%, respectively were produced.  

Technetium-99m sestamibi (MIBI)  
Rizzello V. et al (2005) analysis of 20 studies (488 patients) assessing Technetium-99m sestamibi studies, without the use of nitrates concluded a lower sensitivity of 81%, but better specificity of 66%, with PPV of 71% and NPV of 86%[19]. These results were similar to those by Bax et al (1997), based on meta-analysis of 7 studies with an average sensitivity and specificity of 80% (range 73-100%) and 60% (range 35-86%), respectively. Bax et al (1997) also noticed better results with increased sensitivity from 81% to 91% (range 88-95%) and specificity of 60 to 88% (range 88-89) when nitrates were used. Current practice involves nitrate administration in patients with previous cardiac events.

Limitation and advantages  
The main limitations of SPECT include; higher cost compared to echocardiography, limited spatial resolution, potential difficulty in interpreting results in patients with balanced myocardial ischemia (3-vessel disease) and the risk of radiation. The main advantages include; extensive validation, increasing availability, good sensitivity and lower cost compared to PET.

Prognostic value  
Cardiac SPECT viability study results can predict the recovery of global LV function; 99mTc-sestamibi demonstrated a sensitivity of 81% and specificity of 60%; thallium re-injection a sensitivity of 86% and specificity of 47%; thallium rest redistribution a sensitivity of 90% and specificity of 54%.

Positron Emission Tomography  
Introduction  
Cardiac positron emission tomography (cardiac PET) involves the administration of a tracer, Rubium-82, Ammonium-13, Water-15, and Fluorine-18 deoxyglucose (18-FDP). Of these various positron-emitting radiotracers, which are peripherally introduced, a glucose analogue; Fluorine-18 deoxyglucose (18-FDP), is the most validated radiotracer for cardiac PET metabolism. Glucose 11-C, free fatty acid (FFA), and Oxygen are also metabolism tracers, however glucose is the preferred metabolite for assessment of ischaemic or hypoxic myocardium. The most commonly used criterion to identify viable myocardium is the uptake and metabolism of 18-FDG, which is dependent on viable myocytes, with viable glucose transporters. Viable myocardium displays normal perfusion and normal 18F-FDG uptake, hibernating myocardium displays reduced perfusion and preserved 18F-FDG uptake but, scarred tissue will display no perfusion and absent 18F-FDG uptake.
In order to maximise glucose metabolism, which improves the quality of the images, a glucose fed state, with an insulin infusion for diabetics or those with insulin resistance, is established. Stress testing is not a requirement for a myocardial viability study with cardiac PET.

The recent analysis by Schinkel AF et al (2007) of 24 studies involving 756 patients noted weighted mean sensitivities and specificities of 92% and 63%, and positive and negative predictive values of 74% and 87% respectively. This was confirmed by another review by DiCarlil MF et al (2007), where weighted mean sensitivities of 90% and specificities of 89% were reported. A meta-analysis by Machac J et al (2005) of 8 studies, involving 800 patients, demonstrated slightly higher sensitivities and specificities, 93% and 92%, respectively.

**Limitation and advantages**

The main limitations of PET include its high cost, limited availability, and the use of radio-active tracers. The main advantages include; established validity and excellent sensitivity. Compared with the SPECT, PET has better spatial and temporal resolution, with better quality pictures and less radiation. PET is not limited in patients with devices.

**Prognostic value**

A meta-analysis by Beanlands et al (1998) of 10 studies involving 1046 patients, found that, the mortality rate was higher in those who did not undergo revascularization despite a PET scan confirming significant myocardial viability. The annual death rate was 4% in those that had revascularization versus 17% in those who did not undergo revascularization.

**Magnetic Resonance Imaging**

**Introduction**

The use of cardiac MRI (CMR) in the assessment of myocardial viability is a relatively new concept and therefore does not carry the same clinical evidence advantage as other imaging techniques mentioned above. Despite this, CMR has the potential to overcome limitations presented with other imaging modalities, particularly nuclear imaging, and is therefore of particular interest. Three main techniques employed when using CMR in assessing myocardial viability are; delayed enhancement (DE), known as late-gadolinium enhancement (LGE), dobutamine stress (DS) and end-diastolic wall thickness (EDWT).

The most commonly used DS and EDWT criterion to identify viable myocardium is based on the same principles as in stress echocardiography even the technical dobutamine stress protocol is not different. Viable myocardium demonstrates an increase in contractility, whereas non-viable segments remain unchanged with stress. End-diastolic myocardial thickness is also a marker for viability. DE/LGE techniques demonstrate the status of myocardial perfusion and tissue enhancement by i.v. administration of gadolinium-chelated contrast. After 5min of contrast agent, T1-weighted images are acquired which show regions of myocardial infarction exhibiting high signal intensity i.e. high contrast enhancement. This hyperenhancement is related to the interstitial space between collagen fibers, which is larger in scar tissue/non viable myocardium, than in normal viable myocardium. This allows the determination of the extent of transmural disease, which in turn correlates inversely with the likelihood of functional recovery of the myocardium following revascularization.

A meta-analysis by Romero et al (2012), included 24 prospective trials in 698 patients; 11 studies assessing DE, 9 DS and 4 EDWT. DE demonstrated the highest sensitivity of 95% with specificity of 51%, PPV of 69% and NPP of 90% in detecting viable myocardium. The respective values for DS were 81%, 91%, 93% and 75%. Similar studies suggested the combination of DE and DS to offer more reliable results. Prior to this a cohort of 29 trials demonstrated DE-CMR and PET/SPECT were equally effective in determining myocardial viability. Several studies have supported the latter finding and have additionally demonstrated that DE-CMR is superior to dobutamine stress echocardiography (DSE) in certain patients, particularly those with poor images or arrhythmias.

**Limitation and advantages**

The main limitations of CMR include; high cost, long study time, the requirement for breath-holding sequences and restrictions in patients with implant devices and impaired renal function. However, advances in MRI technology are holding promises to reduce imaging time, increase spatial resolution and adapt to scan implanted devices. The main advantages of CMR include excellent anatomical details using steady state free precision (SSFP) cine sequences in EDWT, good sensitivity/specificity with good interobserver/intraobserver agreement in DE imaging, and excellent sensitivity offered with DS.

**Prognostic value**

Gerber et al (2012) included 144 patients with ischemic LV dysfunction who had undergone DE imaging, then either received revascularization with PCI or CABG or were managed conservatively demonstrated good prediction of survival, which was significantly lower in patients who did not undergo revascularization. Furthermore, it has been suggested that by combining CMR with nuclear imaging additional benefits are obtained. For example, in patients with intermediate DE (25-75%) defined by CMR, PET can assess viable myocardium and determine the likelihood of functional recovery. The use of myocardial tagging has also been shown to increase the efficacy of DS-CMR, increasing its sensitivity and improving the specificity.

**Combined Technology**

Research into manufacturing combined technology is the new approach to overcome many of the limitations of a single imaging technique. One of the techniques is to combine PET and CMR. Whilst CMR defines the transmularity of scars, PET study can characterize the state of the non-scarred subepicardium and help refine the likelihood of functional recovery in cases without too much thickness of scar. By combining the high sensitivity of PET with the high specificity of CMR, an improved diagnosis of difficult cases is achieved. Another technique is using the SPECT imaging cameras to capture the positrons emission from fluorine-18 FDG, as a potential means for combining SPECT and PET. FDG-SPECT compared to other techniques, such as conventional thallium-201 SPECT with re-injection protocol or in combination to low dose dobutamine echocardiography has demonstrated superior predictive values for functional recovery in studies of patients after revascularisation.

**Conclusion**

This review demonstrates the available data, summarised in the table below, which shows high sensitivity for the assessment of myocardial viability for all non-invasive imaging techniques. However, there is a wide range of specificity.
The best data on the clinical impact of myocardial viability assessment comes from a meta-analysis and from two randomised trials; The Surgical Treatment for Ischemic Heart Failure (STICH) trial and The Canadian PPAR study. The meta-analysis of 24 observational studies by Allman et al of varying between 50% and 91%. The recommended approach to assess myocardial viability begins with either dobutamine echocardiography or radionuclide myocardial perfusion imaging, depending upon availability and local expertise. Despite cardiac magnetic resonance (CMR) and positron emission tomography (PET) scanning have greater sensitivity they may be more challenging to perform and not as widely available.

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