Assessment of Myocardial Viability

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Chandra Katikireddy, Nareg Minaskeian, Amir Najafi, and Arang Samim

High Yield Facts

- Viable myocardium refers to dysfunctional myocardium that is expected to recover contractility following revascularization, resulting in improved left ventricular ejection fraction.
- Low dose dobutamine stress echocardiography and dobutamine stress CMR assess the contractile reserve of dysfunctional myocardium and possess high specificity and positive predictive value in diagnosing the myocardial viability.
- SPECT and PET nuclear techniques estimate myocardial perfusion and metabolic activity (^{18}F-FDG PET) to evaluate myocardial viability with a high sensitivity and negative predictive value.
- CMR late gadolinium enhancement (LGE) technique estimates myocardial scar burden accurately.
- Myocardial viability status in ischemic cardiomyopathy may have a prognostic and therapeutic utility with better outcomes in those with viable myocardium treated with optimal medical therapy and coronary revascularization when appropriate.
- In ischemic cardiomyopathy with viable myocardium, according to ACCF/AHA 2013 heart failure guidelines, it is a class IIA recommendation for coronary revascularization if LVEF >35% and class IIA recommendation for either medical therapy or revascularization when LVEF <35%

C. Katikireddy (✉)
University of California, San Francisco, San Francisco, CA, USA

VA Central California Heath Care System, Fresno, CA, USA

Fresno Medical Education Program, Fresno, CA, USA
e-mail: CKatikireddy@fresno.ucsf.edu

N. Minaskeian · A. Najafi · A. Samim
University of California, San Francisco, San Francisco, CA, USA

VA Central California Heath Care System, Fresno, CA, USA

Introduction

Left ventricular systolic dysfunction as a result of coronary artery disease and ischemia portends a poor prognosis from heart failure and arrhythmias.

Hibernating myocardium is a viable, dysfunctional state of the myocardium with a persistently reduced contractility due to reduced coronary blood flow at rest, which may be partially or completely reversible upon revascularization [1]. Stunned myocardium is a dysfunctional state that may persist for a period of time after an episode of transient ischemia despite the restoration of normal blood flow, with spontaneous recovery subsequently [1, 2]. Chronic, repetitive stunning may lead to a hibernating state in myocardium in a short period of time [3]. Non-viable myocardium, as compared to the two former viable states, is the result of irreversible necrosis of the myocytes leading to fibrosis and infarction [1]. It is important to recognize that progression of untreated ischemia and eventual replacement of hibernating myocardium by fibrosis without therapy is a chronic, continuum process [1, 4]. In a chronic state of ischemia, hibernating myocardium can be at early, intermediate or late pre-fibrotic states and success of recovery with therapy and revascularization depends on the stage at which the therapeutic intervention is made.

The following sections provide an overview of assessment of myocardial viability, its therapeutic and prognostic implications as well as management of ischemic cardiomyopathy based on the myocardial viability status.

Assessment of Myocardial Viability

Myocardial dysfunction with impaired contractility is typically termed as 'viable' if it is predicted to recover contractility with medical therapy and coronary revascularization. Viability is estimated by different imaging modalities probing various characteristics of the viable myocardium: end diastolic

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wall thickness on echocardiography (Echo) or cardiac magnetic resonance (CMR), contractile reserve assessment with low dose dobutamine by Echo or CMR, cell membrane integrity based on radioactive tracer uptake on single positron emission computed tomography (SPECT), ischemic myocardial metabolic properties (cellular glucose uptake) by positron emission tomography (PET), and late gadolinium hyper-enhancement (scar) by CMR. Diagnostic accuracy of different imaging modalities in estimating viable status of myocardium is comparable. However, in general, tests (dobutamine Echo and CMR) that evaluate contractile reserve possess higher positive predictive value and specificity, but lower sensitivity compared to those that estimate myocardial perfusion, cell membrane integrity and metabolic properties (SPECT and PET, respectively) which are known to have higher negative predictive value and sensitivity but lower specificity to detect myocardial viability [3–6]. Of note, predominantly, the data comparing the diagnostic accuracy of different imaging tests were not performed in the same subjects.

Commonly used imaging modalities used for viability assessment in the clinical practice (Table 5.1) are described below.

Electrocardiogram (ECG)

The ECG is an initial and useful tool in the evaluation of viability. While the absence of pathologic Q waves may be suggestive of viable myocardium [7] the presence of Q waves is not specific for myocardial infarction. Myocardial hypertrophy, WPW and rarely hibernating myocardium [8] should be considered in the differential diagnoses of pathologic Q waves in addition to myocardial infarction. It would be prudent to consider the presence or absence of Q waves not in isolation but in conjunction with the other imaging markers of myocardial viability status.

Baseline 2D Echocardiography

Myocardial thickness may provide a clue to the viability status. Normal segmental thickness (>6 mm) implies viable myocardium and severely thinned (4 mm or less) segments may be suggestive of non-viable or terminal stages of hibernating myocardium. In a meta-analysis, intact end diastolic wall thickness showed a sensitivity >90% but low specificity of <50% in predicting contractile recovery with therapy [9].

Table 5.1 Comparison of imaging modalities for myocardial viability

Imaging modality	Viability assessment	Sensitivity	Specificity	Advantages	Limitations
DS Echocardiography	Demonstration of contractile reserve	Moderate (70–80%)	High (80–90%)	No radiation No iodinated contrast Quick Routinely available	Higher false-positive rate Moderate positive- predictive value
^{201}Tl MPI SPECT	Normal perfusion (>50% of a normal segment) on redistribution imaging	High (80–90%)	Low to moderate (59%)	Traditionally accepted modality	Time consuming Radiation risk Limited sensitivity
Tc-^{99m} MPI SPECT	Normal perfusion (>50% of a normal segment)	Moderate to high (80–90%)	Moderate (60–70%)	Quicker than ^{201}Tl redistribution imaging Myocardial ischemia and LV function assessed simultaneously	Unable to distinguish 'nonviable' from 'hibernating' myocardium, especially in nontransmural infarcts Radiation risk
^{82}Rb ^{18}F-FDG PET	Perfusion defect with intact metabolism	High (>90%)	Moderate (60–70%)	Superior diagnostic accuracy to SPECT imaging Less radiation Less time consuming	Unable to distinguish subendocardial from transmural infarcts Not routinely available
DS CMR	Presence of contractile reserve	Moderate to high (80%)	High (90%)	Accurately images myocardial scar Superior spatial resolution Differentiates subendocardial from transmural infarct No radiation	Limited outcome data
LGE CMR	Absence of LGE or < 50% transmural extent of LGE with presence of contractile reserve on DS CMR	Moderate to high (80–85%)	Moderate (60–70%)	Superior spatial resolution Less radiation	Hyperenhancement on LGE-CMR may be seen with myocardial necrosis, edema and inflammation

CMR Cardiac magnetic resonance, *DS* Dobutamine stress, *LGE* Late gadolinium enhancement; *^{82}Rb ^{18}F-FDG PET* Rubidium, fluorine fluorodeoxyglucose positron emission tomography, *^{201}Tl MPI SPECT* Thallium myocardial perfusion imaging single photon emission computed tomography

Dobutamine Stress Echocardiography

Stress echocardiography using dobutamine (Fig. 5.1) is a simple, low-risk, non-invasive test with no radiation risk. Myocardial contractile reserve is used as an indicator of viability [3]. Viable, dysfunctional myocardium with contractile reserve in a minimum of >5 segments, increases the success rate of functional recovery following coronary revascularization [10]. Hypokinetic or akinetic hibernating myocardium may demonstrate improved contractility with low dose dobutamine (5–10 μg/kg/min) infusion [1, 11]. At higher doses of dobutamine infusion, hibernating myocardial contractile function may worsen due to ischemia (biphasic response) or continue to improve with no evidence of ischemia. Biphasic response increases specificity (up to 84%) for viable hibernating myocardium [12]. On the contrary, lack of contractile reserve or no ischemic response at higher doses of dobutamine, decreases the specificity.

Single Photon Emission Computerized Tomography (SPECT)

In SPECT imaging, the radionuclide tracer uptake property of the viable cardiac myocyte with an intact cell membrane is used to estimate myocardial viability status. The initial myocardial uptake of 201 Tl (Thallium) is determined by early myocardial perfusion whereas the subsequent uptake over the next 24 h is determined by 'refill and redistribution' of the isotope, determined by the integrity of the cellular membrane [3]. Hibernating myocardium appears as a perfusion defect on early images due to impaired blood flow at baseline but normalizes (at least >50% radioactive tracer uptake of the normal segments) on delayed imaging from redistribution of the 201 Tl. Sensitivity of viability detection on 201 Tl imaging increases in late (24 h) reinjection/redistribution protocols compared to 4 h early redistribution protocol.

Tc^{99m} is dependent on a passive mitochondrial uptake with no redistribution property. When artefactual finding is excluded, perfusion defect at rest on Tc imaging can be either infarct or hibernating myocardium (Fig. 5.2). Further distinction of these fixed perfusion defects can be determined by the presence of wall motion, thickening, and worsening of perfusion defect with stress to some degree in the hibernating myocardium. Even though Tc is considered inferior to Tl imaging due to lack of redistribution feature, studies have shown that both are comparable in diagnostic accuracy of viable myocardial detection [1, 3]. The sensitivity and specificity of ^{201}Tl was demonstrated to be 86 and 59%, respectively, for predicting functional recovery after revascularization and 81 and 66% for Tc^{99m}, respectively [1]. Nitrate administration may increase the sensitivity of viability detection by SPECT.

Positron Emission Tomography (PET)

PET imaging uses the preserved metabolic property of viable myocardium as opposed to the absence of metabolic activity in scar. Superior resolution, quick imaging, absolute quantification of myocardial perfusion and less radiation exposure are the advantages of PET over the SPECT.

Cardiac PET uses Rubidium-82 (^{82}Rb) to assess perfusion and F18-Fluorodeoxyglucose (^{18}F-FDG) to assess myocardial glucose metabolism [1, 3, 4]. Viable myocardium is characterized with reduced perfusion and preserved ^{18}F-FDG up take (Fig. 5.3) [3]. Meta-analyses have indicated a superior diagnostic accuracy of PET in comparison to other modalities to detect viable myocardium [3].

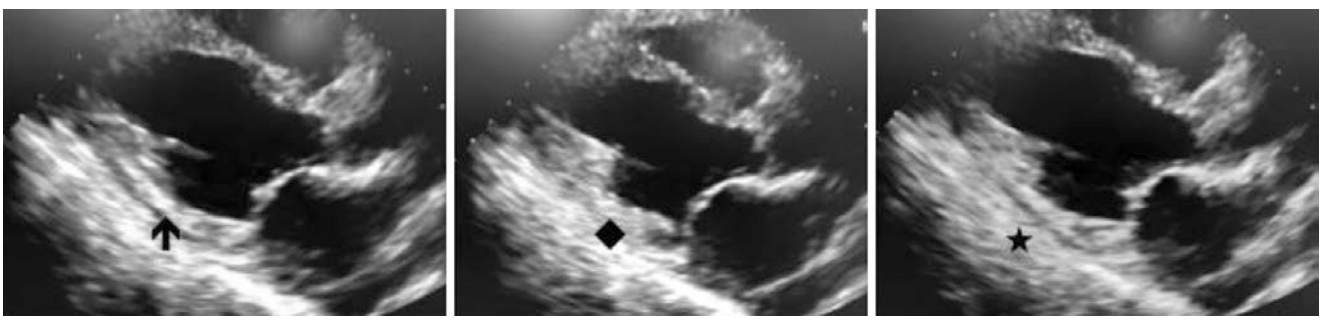

Fig. 5.1 Dobutamine stress Echocardiography demonstrating ischemia and viability (biphasic response) of the inferolateral wall. (**a**) Arrow: Hypokinesis in end systole at baseline; (**b**) Diamond: Improved motion and thickening in systole with low dose dobutamine; (**c**) Star: Hypokinesis at peak dose of dobutamine

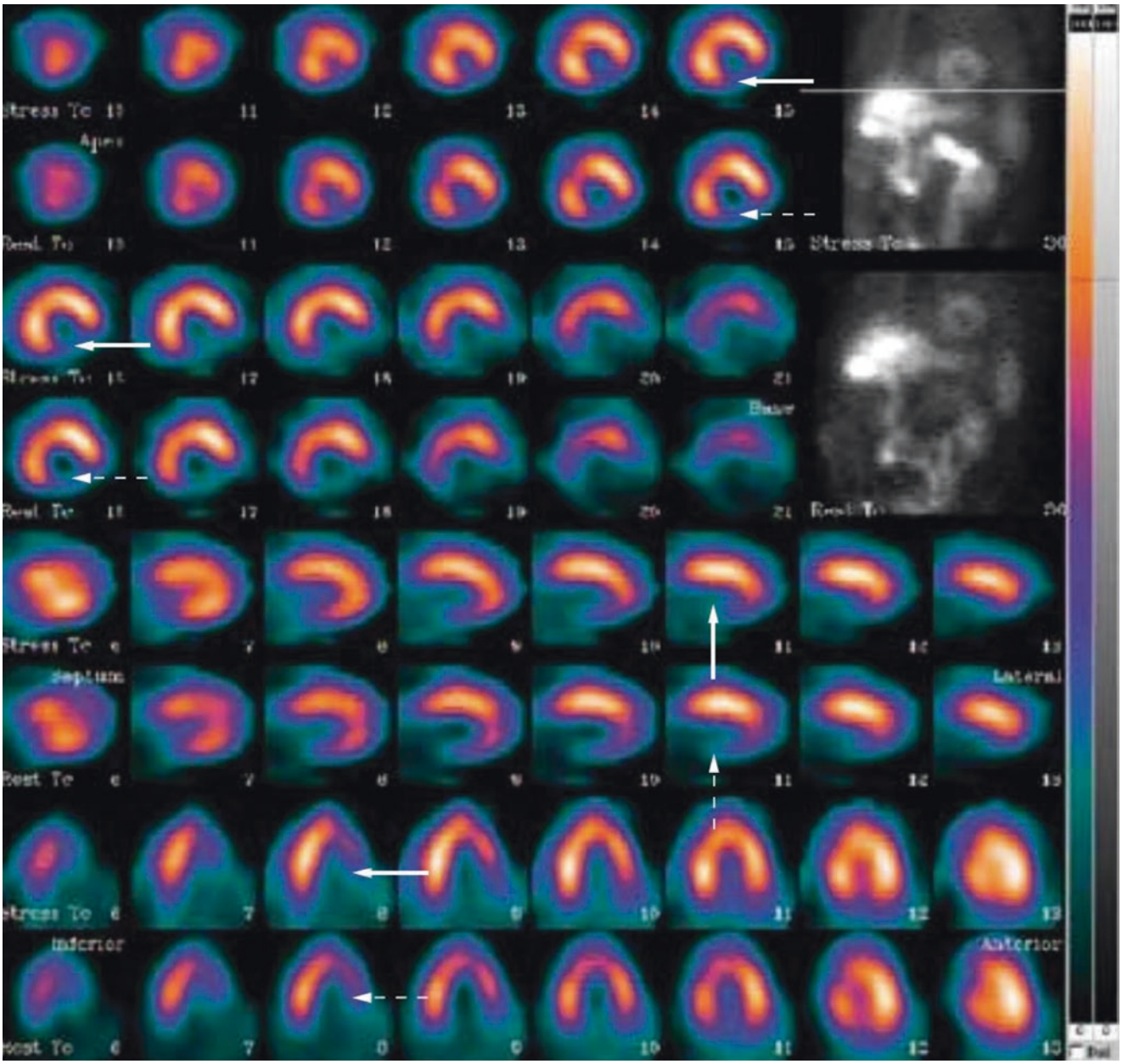

Fig. 5.2 Tc—SPECT imaging showing a fixed perfusion defect in stress (solid arrow) and rest (dashed arrow) imaging of the mid to basal, inferior and inferolateral wall—indicative of scarred, nonviable myocardium

Cardiac Magnetic Resonance Imaging (CMR)

CMR's ability to directly image and estimate the scar burden, myocardial perfusion, segmental wall motion, thickness and contractile reserve with dobutamine infusion, left ventricular ejection fraction, and ventricular volumes [3, 6], makes CMR an ideal test to evaluate myocardial viability in a comprehensive manner.

Gadolinium contrast is rapidly cleared from normal myocardium within 10 min. However, the contrast is trapped in the interstitial space of the scarred myocardium, delaying its clearance and appears bright and enhanced in late gadolinium enhancement (LGE) imaging [13]. Due to superior spatial resolution, CMR can accurately quantify the extent and transmurality of scar tissue and viable myocardium [1]. If transmurality of LGE of a myocardial segment is greater than 50% (Fig. 5.4), it is considered non-viable and is unlikely to recover following revascularization [1, 3, 6]. If LGE is <50% of segmental thickness, myocardium is likely viable, and the diagnostic accuracy of viability can be further enhanced by demonstrating contractile reserve with low dose dobutamine [3]. Integration of multiple viability markers;

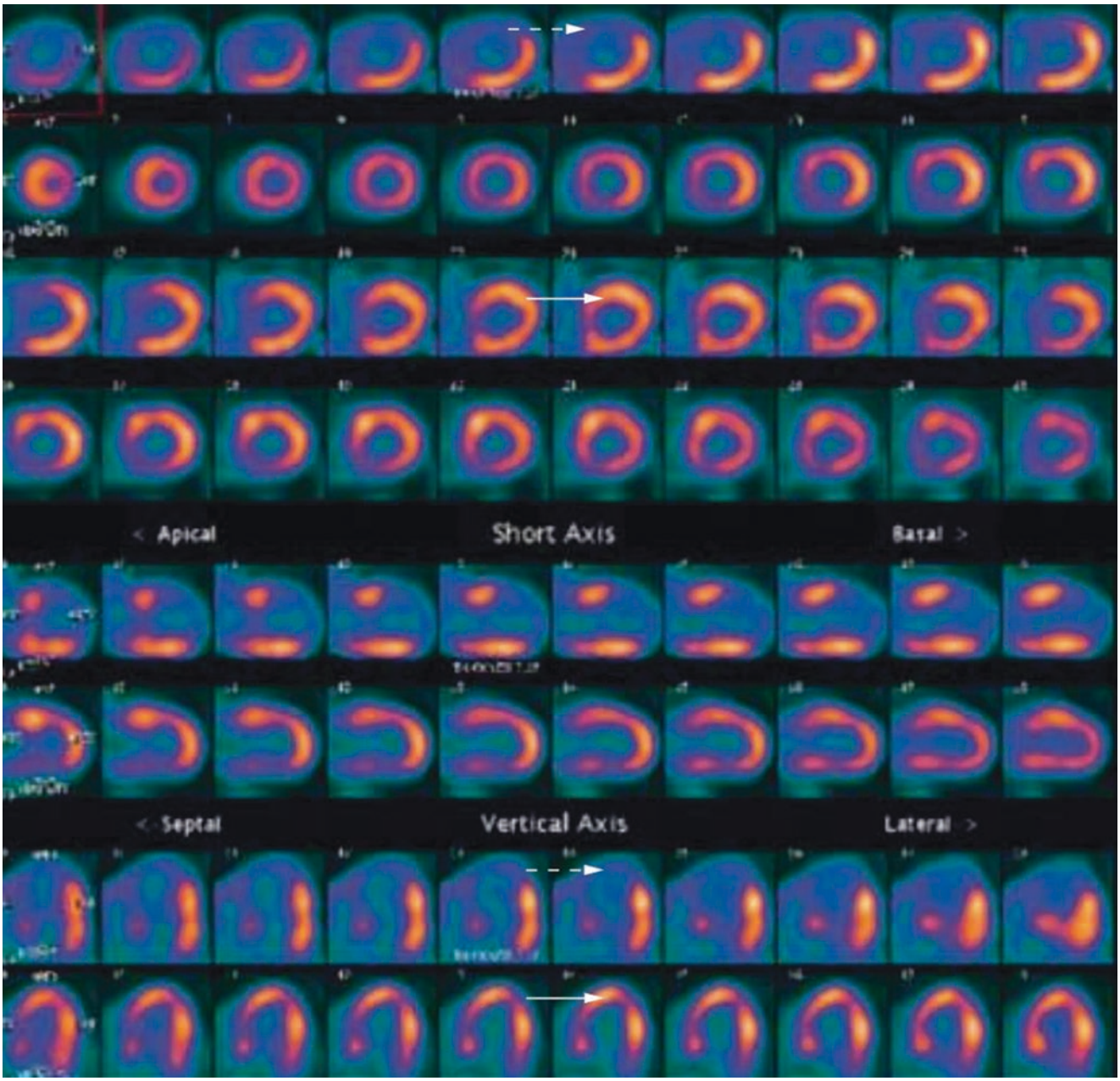

Fig. 5.3 Perfusion defect on ^{82}Rb PET imaging (dashed arrow) shows normal uptake of ^{18}F-FDG demonstrating viable myocardium (solid arrow)

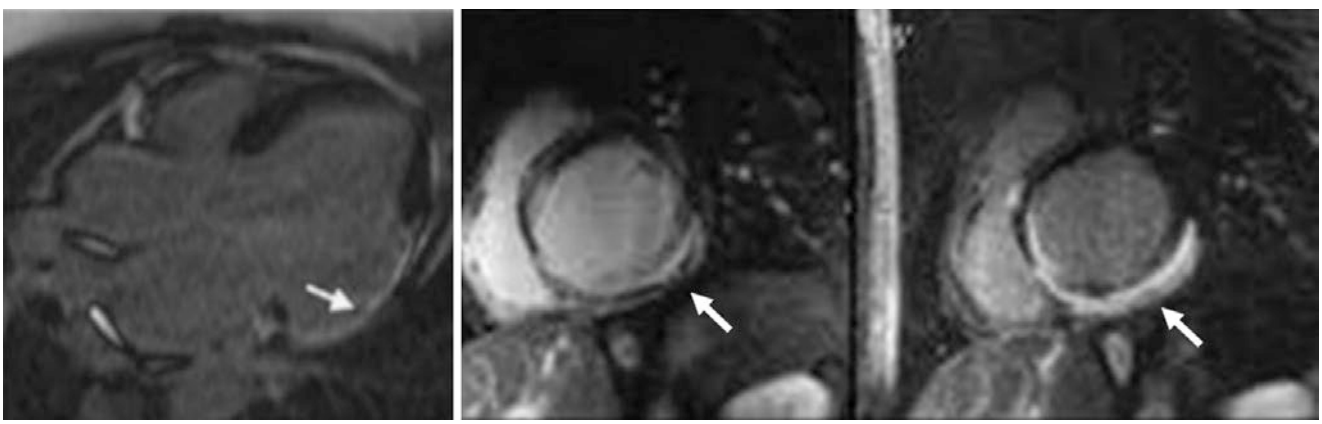

Fig. 5.4 Late gadolinium enhancement (arrow) demonstrates transmural infarct (non-viable myocardium) of the inferolateral and septal segments

end-diastolic segmental thickness, LGE and contractile reserve with dobutamine if necessary would yield a high sensitivity and specificity for determination of viability status [1, 3, 6, 13].

Of note, CMR contraindications such as claustrophobia and implanted devices preclude utility of CMR.

Miscellaneous

Myocardial contrast echocardiography (microvascular integrity assessment), myocardial strain and strain rate imaging by speckle echocardiography and cardiac CT perfusion and late hyper-enhancement (scar) imaging are the modalities [14–16] that have also been shown in studies to estimate myocardial viability with reasonable diagnostic accuracy. However, their use is not in vogue in the mainstream at present due to lack of experience, familiarity and expertise with the technology and non-superiority as compared to the other widely available techniques.

Choice of Viability Test

Choice of test to assess viability depends on several factors including patient's preference, limitations or contraindications of a particular study in a given patient, and local expertise and availability.

The degree of left ventricular (LV) remodeling and dysfunction may play a role in deciding which test to perform. Patients with extreme degrees of LV dilatation and segmental wall thinning are perhaps better served by PET metabolic imaging and CMR delayed enhancement imaging in conjunction with dobutamine stress to evaluate contractile reserve if necessary. In patients with mild to moderate degree of LV dysfunction and remodeling, dobutamine stress Echo and SPECT imaging may suffice.

Clinical Implications of Viability Status in Ischemic Cardiomyopathy

The wealth of evidence suggests that ischemic cardiomyopathy subjects with viable myocardium have a better prognosis with medical therapy and coronary revascularization compared to those with large amounts of scar burden who are at a higher risk for heart failure and ventricular arrhythmias [17, 18]. Most of these studies were under-powered, non-randomized and uncontrolled with inclusion of patients with much heterogeneity in the degree of LV dilatation, systolic dysfunction (ejection fraction), ischemia, and scar burden. Many observational studies and meta-analyses have demonstrated that revascularization of dysfunctional, ischemic, viable myocardium results in improved left ventricular function leading to better clinical outcomes [5, 6]. However, these studies were predated prior to making significant advancements in medical therapy of coronary artery disease (CAD) and cardiomyopathy.

On the contrary, the findings of the STICH (Surgical Treatment of Ischemic Heart Failure) Viability sub-study trial showed no differences in mortality outcomes between the medical versus medical and revascularization therapy groups in severe ischemic cardiomyopathy (LVEF <30%) with no demonstrable interaction between the viability status, surgical revascularization and outcomes. Several limitations of SITCH Viability sub-study are noteworthy. It was non-randomized, non-blinded, underpowered and viability testing was limited to SPECT or dobutamine echocardiography with arbitrary use of the thresholds to define the presence of viable or nonviable myocardium. In addition, it is important to recognize that these results are applicable to only patients with a severe degree of LV dilatation and reduced EF (<30%). In the STICH long-term follow up study however, the surgical revascularization group showed improved 10-year mortality outcomes compared to medical therapy alone, even though immediate, post-op mortality rates were higher [6]. In addition, few other studies have also been found to be supportive of the deterministic nature of the myocardial viability status on clinical outcomes of revascularization in ischemic cardiomyopathy [19].

Over the years, due to the conflicting data as illustrated above, there has been an ongoing debate regarding viability testing and coronary revascularization in patients with ischemic left ventricular dysfunction.

Nevertheless, given the convincing therapeutic and prognostic implications of the myocardial viability status in ischemic cardiomyopathy patients, 2013 ACCF/AHA heart failure management guidelines granted class IIa recommendation for the myocardial viability testing prior to revascularization in ischemic cardiomyopathy [7].

Coronary Revascularization in Ischemic Cardiomyopathy

Currently, the approach of therapy in ischemic cardiomyopathy is guideline based and widely accepted in clinical practice. First and foremost, it is essential to ensure everyone receives optimal guideline directed medical therapy.

Surgical revascularization has been shown to improve the mortality outcomes in patients with CAD and LV dysfunction with viable myocardium [18]. No mortality benefit was observed with percutaneous intervention, partly due to exclusion of high-risk patients such as left main disease, utilization of the older generation stents, and sub-par medical therapy.

In general, hibernating myocardium of approximately 20% of LV mass may be needed to make a meaningful impact in LV function (at least >5% improvement in LV ejection fraction) after revascularization [20]. On the same token, when myocardial scar is >20% of LV myocardium or the number of scar segments >4, success of LV global functional recovery with revascularization is less likely [21]. LV function improvement following the revascularization therapy may take from 6 months to a year or even longer in severely dysfunctional cases [22].

Viable, dysfunctional myocardium can be a wide spectrum from early stages of hibernation with minimal LV remodeling to late, pre-fibrotic state with ultra-structural changes of the cytoskeleton, manifesting as severe LV remodeling and segmental wall thinning [1]. Several factors may determine the recovery of contractile function and LV remodeling. As the degree of ischemia, extent of viable myocardium, and segmental wall thickness and LV ejection fraction increase with less of adverse LV remodeling, the chances of successful contractile recovery following the coronary revascularization may be high. On the contrary, viable myocardial segments in an adversely remodeled LV with thinned walls and severely reduced ejection fraction in association with large degree of scar burden may have less chances for the contractile improvement after the revascularization [18].

In ischemic cardiomyopathy with advanced LV systolic dysfunction, it is essential to optimize medical therapy and take a multitude of factors; presence or absence of angina, degree of myocardial ischemia, extent of the viable and nonviable myocardium, LV adverse remodeling, LV ejection fraction, patient's comorbidities and procedural risk into consideration prior to coronary revascularization.

As per ACCF/AHA 2013 heart failure guidelines, if the myocardium is viable, it is a class IIA recommendation for coronary revascularization if LV ejection fraction >35% and class IIA recommendation for either medical therapy or revascularization when LV ejection fraction <35% [23]. Revascularization may be considered in patients with an LV ejection fraction <35% and viable myocardium, if patients remain symptomatic on optimal medical therapy with an acceptable procedural risk and optimal coronary anatomy for the surgical or percutaneous intervention. Time to recovery can be delayed in these patients and it is not uncommon to take over a year in those with poor baseline characteristics [22].

Conclusions

In ischemic cardiomyopathy with mild to moderate systolic dysfunction and viable myocardium, coronary revascularization is recommended in addition to optimal medical therapy. In advanced ischemic cardiomyopathy with an LV ejection fraction <35% if the myocardial segments of diseased coronary territories are viable, revascularization should be considered, especially when there is no substantial improvement on optimal medial therapy alone. Patient's procedural risk and comorbidities must be considered. In this group of patients, further research is needed to determine the viability status with confidence and predict those who could benefit from coronary revascularization with improved LV function and better outcomes.

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