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Multimodality Imaging of Myocardial Viability

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Abstract

Purpose of Review Myocardial viability is an important pathophysiologic concept which may have significant clinical impact in patients with left ventricular dysfunction due to ischemic heart disease. Understanding the imaging modalities used to assess viability, and the clinical implication of their findings, is critical for clinical decision-making in this population.

Recent Findings The ability of dobutamine echocardiography, single-photon emission computed tomography, positron emission tomography, and cardiac magnetic resonance imaging to predict functional recovery following revascularization is wellestablished. Despite different advantages and disadvantages for each imaging modality, each modality has demonstrated reasonable performance characteristics in identifying viable myocardium. Recent data, however, has called into question whether this functional recovery leads to improved clinical outcomes.

Summary Although the assessment of viability can be used to aid in clinical decision-making prior to revascularization, its broad application to all patients is limited by a lack of data confirming improvement in clinical outcomes. Thus, viability assessments may be best applied to select patients (such as those with increased surgical risk) and integrated with clinical, laboratory, and imaging data to guide clinical care. Future research efforts should be aimed at establishing the impact of viability on clinical outcomes.

Keywords Viability · Hibernating myocardium · Dobutamine echocardiography · SPECT · CMR · PET

Introduction

The concept of myocardial viability is predicated on the clinical observation of improvement in contractility of

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dysfunctional myocardium following reperfusion (i.e., coronary revascularization). This can be described in both the acute and chronic settings. During an acute ischemic insult, contractile function of noninfarcted myocardium is often impaired, even after successful revascularization [1]. This impairment, or myocardial "stunning," may persist for hours, days, or even weeks, but will typically recover. In the setting of chronic ischemia, perhaps in the form of repeated subclinical ischemic insults, myocardium also becomes dysfunctional [2, 3]. Although not infarcted, this "hibernating" myocardium may remain dysfunctional for years, and may become thinned, akinetic or even dyskinetic [4]. Hibernating myocardium, by definition, is expected to improve contractile function following revascularization. At the cellular level, stunned or hibernating myocardium is associated with several ultrastructural changes including loss of sarcomeres, accumulation of glycogen, and loss of sarcoplasmic reticulum [5].

Since the presence and extent of viable myocardium can predict the likelihood of contractile recovery following revascularization, the noninvasive assessment of viability may be an important tool in clinical decision-making. Specifically, in patients with myocardial dysfunction due to ischemic heart disease, the presence or absence of viability may help guide the decision to pursue revascularization or influence the method of revascularization. In this review, we outline the attributes of noninvasive imaging modalities for the assessment of myocardial viability and the implication for clinical practice.

Echocardiography

Dobutamine echocardiography (DE) is a widely available imaging technique that can be used to assess for viability in dysfunctional myocardium [6]. Dobutamine is an adrenergic agonist that acts on beta-1 adrenergic receptors to increase cardiac contractility and heart rate, and on beta-2 adrenergic receptors to cause peripheral vasodilation [7].

For the assessment of viability, dobutamine infusion should be initiated at a relatively low dose (e.g., at 5 µg/kg/ min), with incrementally increasing infusion doses of up to 20–40 µg/kg/min [8]. At low doses, hibernating myocardium will typically augment contractile function. At progressively higher doses, this hibernating myocardium may become hypokinetic or akinetic, due to flow-limiting stenosis in the setting of increased metabolic demand. This "biphasic response" indicates viable myocardium and is most predictive of post-revascularization functional recovery [9]. Other responses generally indicate a lack of viability, although sustained improvement may suggest a partial thickness infarction (i.e., not transmural) with a small possibility of improvement in function [9]. While large prospective studies are lacking, approximate sensitivity and specificity for improvement in regional function after revascularization range from approximately 75 to 80% and 80 to 85%, respectively [8]. For prediction of overall improvement in global function, demonstration of viability has a high sensitivity (86 to 90%) and moderate specificity (71% to 90%), with greater recovery being associated with a more positive response to dobutamine. A minimum of 4 or 5 viable segments is needed to predict a significant improvement in left ventricular ejection fraction (LVEF) [10].

Other Echocardiographic Techniques

Several other echocardiographic techniques have demonstrated potential usefulness for assessing viability. First, the measurement of end diastolic wall thickness alone (< 6 mm) was shown to be highly predictive of a lack of viability [11]. However, Shah and colleagues called this finding into question when they demonstrated that 18% of thinned myocardial segments had evidence of viability by cardiac magnetic resonance (CMR) and recovered function after revascularization [4]. The use of intravenous echo contrast can improve accuracy of DE studies by improving endocardial resolution in patients with limited acoustic windows. Echo contrast can also be used to evaluate myocardial perfusion and quantify myocardial resting blood flow [12]. The use of echo contrast for this purpose has not been approved by the United States Food and Drug Administration and has not achieved widespread use in the USA. Finally, tissue Doppler imaging, strain, and strain rate have all been shown to be able to distinguish viable from nonviable myocardium, and recent guidelines recommended their use be considered an adjunct to visual assessment [8].

Advantages of echocardiography include its lower cost and general availability, in addition to the lack of ionizing radiation or renal toxicity. Limitations include technical difficulties in acquiring images in patients with poor acoustic windows, although contrast administration can mitigate this limitation. Image interpretation of DE is subject to reader variability, especially in patients with limited image quality [13].

Single-Photon Emission Computed Tomography Imaging

Several properties make thallium-201 (TI-201) well-suited for the evaluation of myocardial viability. As an analog of potassium, which is present in myocytes and nearly absent in scar, TI-201 can be used to differentiate between viable and nonviable myocardium [14]. TI-201 has a high first-pass extraction that is proportional to coronary blood flow. Uptake into the myocyte peaks within 5 min of injection and occurs via the Na+/K+-adenosine triphosphate (ATPase) transport system and facilitative diffusion [15]. Retention of TI-201 requires an intact sarcolemmal membrane. Redistribution begins about 15 to 20 min after injection and is related to clearance from the myocardium via the concentration gradient between intracellular and circulating Tl-201. Thallium uptake, retention, and redistribution are determined by myocardial perfusion, sarcolemmal membrane function, and myocyte metabolic activity, which are the underpinnings of myocardial viability.

The two main protocols that utilize TI-201 to assess for myocardial viability, rest- and stress-redistribution, take advantage of these properties. In the rest-redistribution protocol, TI-201 is injected at rest, and imaging occurs at 10 to 15 min. Redistribution images are obtained 4 h later. Myocardial segments with a perfusion defect on rest images may have increased Tl-201 uptake at 4 h. If Tl-201 uptake increases by at least 10%, the segments are deemed viable and likely to recover function with revascularization [16] (Fig. 1). In the stress-redistribution protocol, if an assessment of ischemia is needed, TI-201 can be injected just prior to peak exercise or at peak pharmacologic vasodilatation. Stress imaging is obtained at 15 min. Rest images are obtained at 2.5-4 h. If a fixed perfusion defect is noted, redistribution images are obtained after a 24-h delay which may include re-injection of 1-2 mCi Tl-201 [17].



Fig. 1 Thallium rest-redistribution short-axis images. Resting perfusion (top row) showing a defect in the apical septum, mid anteroseptum, and inferior walls (*arrows*). On redistribution (bottom row), there is increased tracer in the apical septum and mid anteroseptum (*arrows*), consistent

with viability in the distribution of the left anterior descending artery. Lack of tracer on redistribution images in the inferior wall (*stars*) suggests myocardial scar (i.e., no viability)

While individual studies have reported variable performance characteristics for Tl-201 imaging, one meta-analysis reported a mean sensitivity of 87% and a specificity of 54% for the prediction of regional recovery of LV function following revascularization [18].

Technitium-99m (Tc-99m) labeled tracers, such as sestamibi and tetrofosmin, are most commonly used in the evaluation of ischemia, but can also be utilized to assess for myocardial viability. Tc-99m is a lipophilic, cationic compound that enters myocytes via passive diffusion. Unlike Tl-201, redistribution of Tc-99m is limited. Uptake and retention of Tc-99m require intact mitochondrial and sarcolemmal membranes, which are key determinants of myocyte viability. Tc-99m sestamibi has been shown to be comparable to Tl-201 in its ability to predict regional recovery of function following revascularization [18, 19]. The addition of a short-acting nitrate prior to administration of Tc-99m sestamibi may improve sensitivity [20, 21]. Both Tl-201 and Tc-99m sestamibi have class I indications for use in the assessment of myocardial viability [22].

The use of SPECT imaging to detect myocardial viability has two important advantages over other modalities widespread availability and virtually no contraindications. Disadvantages include ionizing radiation exposure and the need for serial imaging, which prolongs testing time. SPECT imaging also has low spatial resolution and is prone to attenuation artifacts, particularly with Tl-201, which emits lower energy photons than Tc-99m [23]. The addition of low-dose CT imaging, however, can mitigate artifacts caused by attenuation. Finally, viability within a segment is often interpreted as being "all or none" with SPECT imaging [24]. Quantitative methods have been developed and validated to assess for myocardial viability [25]; however, the majority of studies are interpreted qualitatively.

Positron Emission Tomography

Positron emission tomography (PET) uses both perfusion and metabolic imaging to evaluate for myocardial viability.

Perfusion imaging is performed at rest (although stress images can be obtained if needed) and typically uses nitrogen-13 ammonia or rubidium-82 as perfusion agents. Although not approved by the United States Food and Drug Administration, oxygen-15-labeled water is frequently used outside of the USA. For metabolic imaging, PET relies on glucose metabolism using a radiolabeled fluorine-18 deoxyglucose (FDG). Prior to FDG imaging, careful attention must be paid to patient preparation, including patient fasting for at least 6 h, followed by an oral (or intravenous) glucose load. This will stimulate endogenous insulin release to help minimize the variability in substrate environment between patients [26]. Following the glucose load, insulin can be administered as needed.

Recognizing the various regional uptake patterns of FDG compared with regional myocardial perfusion allows for differentiation between normal, stunned, hibernating, and nonviable myocardium:

- Hibernating myocardium: "PET mismatch" or "perfusion metabolic mismatch" in which the presence of preserved FDG uptake in regions of decreased blood flow indicates hibernating or viable myocardium (Fig. 2a).
- Nonviable myocardium: "PET match" in which there is concordant reduction in both metabolism and flow. This indicates replacement fibrosis/scar (Fig. 2b).
- Stunned myocardium: Regional dysfunction in the setting of normal perfusion and metabolism.
- Normal myocardium: Normal FDG and normal perfusion.

In addition to these, normal perfusion with reduced FDG ("reversed perfusion-metabolism mismatch") can be seen in the septum in patients with left bundle branch block [27]. It should also be noted that partial reduction in perfusion with normal FDG uptake may indicate partial thickness (i.e., nontransmural) scar.

Many studies have reported the performance of PET for predicting functional myocardial recovery after revascularization. In a meta-analysis of 20 studies with 598 patients undergoing PET followed by revascularization, PET had a mean



Fig. 2 PET perfusion/metabolic images from 2 different patients. **a** Perfusion images indicating a large anterior/septal defect (*arrows*). Corresponding metabolic (FDG) images showing metabolic activity throughout the anterior/septal regions, suggesting viable myocardium in the distribution of the left anterior descending artery. **b** Perfusion images



indicating a large perfusion defect in the distribution of the left anterior descending artery (*arrows*). Corresponding metabolic (FDG) images showing no metabolic activity in segments with perfusion defects, indicating no viability (i.e., scar)

sensitivity of 93% and specificity of 58% for predicting segmental functional recovery [28]. The extent of viable myocardium (or conversely, scar) on PET has been shown to predict the magnitude of improvement in LVEF, as well as symptoms after revascularization [29–31].

Compared to SPECT imaging, PET has better spatial resolution and is less prone to attenuation artifact. A significant limitation of PET is high cost and the lack of widespread availability, particularly of PET myocardial perfusion agents. The latter require either a cyclotron or on-site generators. Therefore, some centers employ hybrid techniques that combine metabolic assessment of FDG with perfusion imaging using SPECT to assess viability [32]. In addition, viability assessment with FDG PET/CT in diabetic patients requires more complex protocols and does not perform as well as in the non-diabetic population.

Cardiac Magnetic Resonance Imaging

CMR is an important modality for the assessment of myocardial viability. The most commonly used CMR technique to determine viability is late gadolinium enhancement (LGE), sometimes referred to as hyperenhancement or delayed hyperenhancement. This technique requires the use of intravenous gadolinium-based contrast agents, whose magnetic properties differ from blood and myocardial tissue, allowing for easy detection by CMR. To acquire images for LGE assessment, gadolinium is injected intravenously and followed by image acquisition approximately 10–20 min after injection [33]. Since gadolinium accumulates in injured or scarred myocardium, but not in healthy myocardium, CMR can reliably distinguish between them. Gadolinium can accumulate in necrotic tissue and in acutely injured myocytes intracellularly, as it can pass through damaged cell membranes. In chronic myocardial scar, gadolinium accumulates in the increased extracellular space that results from replacement fibrosis [34].

Due in part to its superior spatial resolution, CMR can detect infarcts involving as little as 2 g of myocardial tissue [35]. Thus, unlike other imaging modalities, CMR can directly visualize subendocardial infarctions and can accurately quantify the transmural extent of LGE. It is this transmural extent of LGE that is used to determine viable versus nonviable myocardium, with an increasing proportion of LGE indicating less viability (Fig. 3). This was demonstrated in a landmark study by Kim and colleagues in which the presence of viability, as determined by improvement in regional contractile function, was demonstrated in a stepwise fashion based on the transmural degree of LGE [36•]. While a cutoff value of < 50% transmural LGE is often employed to indicate viability, it is important to highlight that CMR, unlike other imaging modalities, can predict viability based on a continuum of the likelihood of recovery, rather than a binary determination [37].

Another advantage of CMR over other imaging modalities is the ability to evaluate viability even in thinned-out myocardium. The measurement of end diastolic wall thickness itself can be used to assess for viability, with wall segments measuring < 5.5 or 6.0 mm classified as nonviable [38, 39]. Shah and colleagues, however, demonstrated that even in markedly thinned (< 5.5 mm), akinetic or dyskinetic myocardium, the absence of significant LGE may indicate viable tissue [4]. In this study, 18% of thinned myocardial segments showed limited LGE, which was associated with improved contractility and resolution of wall thinning. This contradicted the notion that thinned-out myocardium invariably indicates nonviable tissue. Importantly, other modalities such as SPECT or PET



Fig. 3 CMR-LGE images from 4 different patients, all with ischemic myopathies and reduced left ventricular ejection fractions, showing different grades of scar/viability. **a** and **b** 4- and 2-chamber images showing absence of LGE (i.e., uniformly dark/black myocardium), suggesting high likelihood of recovery of function following revascularization. **c** 2-chamber image with minimal (<25% transmural thickness) LGE/scar of the inferior wall (*arrows*) also suggesting high likelihood functional recovery following revascularization. **d** 2-chamber

imaging, lack the spatial resolution to determine viability in thinned wall segments or to detect thinner endocardial infarctions [40].

Although less commonly used, dobutamine CMR can also be employed to determine viability. This technique uses cine imaging both at rest and during the administration of dobutamine. Similar to dobutamine echocardiography, the presence or absence of viability depends on the contractile response of each wall segment during dobutamine infusion [38]. When used in conjunction with LGE, dobutamine CMR may help improve the sensitivity of viability testing [39].

Determining precise sensitivity/specificity of CMR is problematic for several reasons. First, as mentioned, CMR can measure LGE on a continuum. Thus, altering cutoff values will change sensitivity/specificity estimations [39]. Additionally, partial thickness infarction (i.e., 25–75% transmural extent) may take more than 6 months to recover function after revascularization, as demonstrated by Kirshbaum and colleagues who showed continued improvement at 3 years [41]. Nonetheless, when using a binary cutoff of 50% transmural extent of LGE, one meta-analysis showed excellent sensitivity (95%) with limited specificity (51%) for CMR determination of viability.

image demonstrating a large area of scar/LGE in the left anterior descending distribution (*arrows*), but with nontransmural (i.e., just under 50% transmural thickness) involvement, suggesting possible, but less likely, functional recovery following revascularization. \mathbf{e} 4-chamber image with transmural scar throughout the left ventricular apical segments (*arrows*), indicating extremely low likelihood of functional recovery with revascularization

Limitations of CMR include the lack of widespread availability. Additionally, some implanted medical devices are not compatible with CMR. It should be noted that "MR conditional" implanted cardiac rhythm devices (e.g., pacemakers and defibrillators) are being increasingly used, allowing for CMR compatibility. Even patients with devices long thought to be contraindicated for CMR are now undergoing CMR routinely at select centers [42]. It should be noted, however, that even when these devices can be imaged safely, they may cause significant imaging artifact. Finally, while the use of newer gadolinium-based contrast agents may be safer in patients with renal impairment, there remains some concern for nephrogenic systemic sclerosis in patients with very poor renal function (i.e., GFR < 30).

Cardiac Computed Tomography

The detection of infarction by CT was described several decades ago [43]. More recently, electrocardiogram-synchronized, contrast-enhanced, multidetector CT has shown the ability to measure late contrast enhancement, analogous to LGE by CMR [44, 45]. While CT images are limited by poor signal to noise ratio compared to CMR, limited data suggest a reasonable performance when compared with other modalities [46]. Thus, the use of computed tomography for estimating viability warrants continued investigation.

Performance Characteristics and Comparison of Modalities

Quantifying performance characteristics (e.g., sensitivity/ specificity and positive/negative predictive values) for each modality is challenging. One major limitation is the lack of standardization of methodology for each imaging technique. Another issue is that the most commonly used "gold standard" for assessment of viability is recovery of contractile function following revascularization, which raises multiple methodological concerns. For example, one important question raised is how long after revascularization is long enough to see maximal improvement of viable myocardium? Many studies use 2-6 months, but this has been shown to be inadequate for improvement in some segments (i.e., those with partial thickness/nontransmural scar) [9, 47]. Also, evaluation of functional improvement is subjective and may be difficult to assess on a segmental basis, especially in segments that have only partial improvement and/or are not well visualized. Furthermore, a binary prediction of improvement may be less appropriate for modalities that can provide likelihood of recovery on an incremental or continuous scale (e.g., CMR). Finally, as discussed below, it is not clear that functional recovery after revascularization is even an appropriate standard, since clinical outcomes (e.g., cardiovascular events, survival) may not be directly associated.

Given some of these methodologic difficulties, it is not surprising that there is significant variability between individual studies reporting accuracy, many of which have relatively small sample sizes. Although limited by these variable data, meta-analyses provide some estimation of performance of each modality and are summarized below (Table 1).

Similar to the difficulties evaluating each modality, comparisons between modalities can be difficult to assess. Studies performing different imaging modalities in the same patients are ideal, but less frequently undertaken. In one meta-analysis (563 patients) that included only studies that used both nuclear (PET or thallium SPECT) and DE in each patient, nuclear imaging showed higher sensitivity (83% versus 79%), while DE showed higher specificity (79% versus 63%) [48]. Later meta-analyses have supported this finding (Table 1) [18]. When comparing nuclear techniques, PET appears to have a slight advantage over thallium and technetium-99m, particularly with regard to sensitivity and negative predictive value [18]. LGE-CMR has excellent sensitivity and negative predictive value with more limited specificity [39]. With the limitations of these comparative data, there is no universal recommendation that can be made as to which modality should be used in all cases. In clinical practice, the modality chosen often depends upon availability and local expertise. Certain patient populations may be better suited for a given modality. Some examples include patients with severe renal disease or certain implanted devices may wish to avoid LGE-CMR; those with arrhythmic concerns might avoid dobutamine studies; and patients with poor acoustic windows are not ideal for echocardiographic evaluation.

The potential advantages of having a patient undergo multiple imaging modalities to increase accuracy have been advocated by some [49], although cost and increased testing burden are among the obstacles for this strategy. Newer hardware systems, such as PET/MRI machines, have the advantage of combining multiple modalities in a single acquisition protocol and warrant further investigation [50], but access to these systems in current practice is limited.

Clinical Implications

As outlined above, there is ample evidence confirming the ability of DE, SPECT, PET, and CMR to predict improvement of LV regional and global (i.e., LVEF) function following revascularization. Thus, the primary role of viability has been as a tool to assist in the clinical decision of whether or not to recommend revascularization to patients with LV dysfunction due to ischemic heart disease. In some cases where revascularization is clearly warranted, viability is used as a guide to determine the method of revascularization (e.g., percutaneous coronary intervention versus coronary bypass grafting). While it is a reasonable assumption that improvement in LV function would positively impact clinical outcomes, convincing evidence to support this has been lacking.

Several retrospective studies have suggested favorable clinical outcomes for those with viability who undergo revascularization versus those that do not [51]. Some prospective observational studies also supported this finding. For example, Gerber and colleagues found that patients with myocardial viability on CMR that underwent revascularization had better survival compared with those treated with medical therapy. Patients with no viable myocardium had similar outcomes whether or not they were revascularized [47]. Interestingly, among those who were not revascularized, the subjects with viable myocardium had increased mortality. One possible explanation for this is that viable but dysfunctional myocardium may be arrhythmogenic, leading to increased arrhythmias and sudden death [47, 52, 53].

These findings of improved outcomes following revascularization have not been consistently reproduced. The largest clinical study to investigate the impact of viability on clinical outcomes was the STICH viability substudy [54•] along with Table 1Performancecharacteristics of noninvasiveimaging modalities for predictingregional recovery of functionfollowing revascularization

Method	Patients, n	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Db-echo	1421	80	78	85	83
²⁰¹ TI	858	87	54	67	79
^{99m} Tc	488	83	65	74	76
PET- ¹⁸ F-FDG	598	92	63	74	81
LGE-CMR	331	95	51	69	90
Db-CMR	247	81	91	93	75

Db-CMR, dobutamine cardiovascular magnetic resonance; *Db-Echo*, dobutamine echocardiography; *LGE-CMR*, late gadolinium-enhanced cardiovascular magnetic resonance; *PET-FFDG*, positron emission tomography-fluorodeoxyglucose; *NPV*, negative predictive value; *PPV*, positive predictive value; *Tc*, technetium-99m; *Tl*, thallium-201

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the STICH viability long-term follow-up study [55•]. The STICH trial was a multi-center, non-blinded, randomized controlled trial that included 1212 patients with ischemic cardiomyopathy, and compared one group treated with optimal medical therapy and coronary artery bypass surgery compared to optimal medical therapy alone [56]. At 10-year follow-up, there was a significant reduction in all-cause mortality with the addition of coronary bypass surgery [57]. The viability substudy was a nonrandomized, observational study that evaluated the impact of viability in 601 patients, as measured by DE and thallium SPECT, on clinical outcomes. The presence of viability was associated with an improvement in LVEF regardless of treatment group (i.e., coronary bypass surgery versus medical alone) at 10-year follow-up. However, the improvement in clinical outcomes (i.e., survival) demonstrated with coronary bypass surgery was not affected by the presence or absence of myocardial viability.

A number of methodologic limitations have been raised with regard to STICH viability [58, 59]. Among the criticisms were the lack of randomization, the presence of angina in the majority of subjects, and the definition of viability. For thallium SPECT, viability was defined as adequate tracer uptake in at least 11 segments (65% of myocardium) regardless of whether those segments were dysfunctional, meaning "normal" segments would have been included as viable. Others have suggested that if CMR or PET was used, results may have been different [59], although this was not borne out in one of the few randomized studies, the PARR-2 trial [60•]. In PARR-2, subjects were randomized to viability testing with PET versus no viability testing prior to revascularization and clinical outcomes were assessed following treatment (which included medical therapy with or without revascularization). In both the initial results of this study and the longer term follow-up [61], no benefit on outcomes was shown in the PET group. Interestingly, the subset of subjects who followed the recommendations from the PET viability results as whether to undergo revascularization or not did show a significant improvement in outcomes $[60^{\bullet}, 62]$.

Despite the concerns regarding STICH methodology, it remains the largest prospective study to date for viability assessments of clinical outcomes. Along with other inconsistent data regarding viability and outcomes [63], the STICH data argue against the widespread use of viability testing for patients with ischemic heart disease undergoing consideration for revascularization. Nonetheless, it remains reasonable to consider viability testing in select patients. For example, viability assessment may be considered for patients who might benefit from revascularization but have high operative risk due to age and/or comorbidities.

Conclusions

Dobutamine echocardiography, SPECT, PET, and CMR are all well-established imaging modalities for the assessment of myocardial viability. While they each exhibit different advantages and disadvantages, no single modality can claim clear superiority. Despite data confirming the improvement in LV function following revascularization in patients with viable (versus nonviable) myocardium, there remains no definitive data that clinical outcomes improve. Thus, viability testing to aid planning for revascularization may be best used selectively (e.g., in those with increased surgical risk), and integrated with comprehensive clinical, laboratory, and imaging data. Future investigation focusing on clinical outcomes in this population is warranted.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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