Circulation: Cardiovascular Imaging

AHA SCIENTIFIC STATEMENT

State of the Art: Imaging for Myocardial Viability

A Scientific Statement From the American Heart Association

Endorsed by the Society for Cardiovascular Magnetic Resonance

ABSTRACT: A substantial proportion of patients with acute myocardial infarction develop clinical heart failure, which remains a common and major healthcare burden. It has been shown that in patients with chronic coronary artery disease, ischemic episodes lead to a global pattern of cardiomyocyte remodeling and dedifferentiation, hallmarked by myolysis, glycogen accumulation, and alteration of structural proteins. These changes, in conjunction with an impaired global coronary reserve, may eventually become irreversible and result in ischemic cardiomyopathy. Moreover, noninvasive imaging of myocardial scar and hibernation can inform the risk of sudden cardiac death. Therefore, it would be intuitive that imaging of myocardial viability is an essential tool for the proper use of invasive treatment strategies and patient prognostication. However, this notion has been challenged by large-scale clinical trials demonstrating that, in the modern era of improved guideline-directed medical therapies, imaging of myocardial viability failed to deliver effective guidance of coronary bypass surgery to a reduction of adverse cardiac outcomes. In addition, current available imaging technologies in this regard are numerous, and they target diverse surrogates of structural or tissue substrates of myocardial viability. In this document, we examine these issues in the current clinical context, collect current evidence of imaging technology by modality, and inform future directions.

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Ischemic heart disease affects >110 million individuals worldwide and increased by 73.3% from 1990 to 2015.[1] Despite modern therapies, up to one-third of patients with acute myocardial infarction (MI) will develop heart failure.[2] This increasing health burden has been attributed to increased patient survival and the overall aging of the population, 2 prevalent trends in the health landscape. The prevalence of ischemic heart failure was 270 per 100 000 person-years in men and 190 per 100 000 person-years in women in 2010.[3]

Ischemic cardiomyopathy is associated with a spectrum of histological changes, depending on the ischemic insult and adaptive mechanisms. When blood supply to the myocardium is abruptly interrupted, necrosis of cardiomyocytes starts rapidly, with 13% necrotic cardiomyocytes noted in the area at risk after 30 minutes of left anterior descending (LAD) artery ligation in rats.[4] During the first hours after a severe ischemic insult, multiple pathways are activated, including inflammatory pathways and metalloproteinases, leading to replacement of the necrotic myocardial tissue by an irreversible fibrotic scar. With lesser degrees or duration of blood flow reduction, however, the myocardium may remain viable, in a state of hibernation or stunning, potentially regaining its function after revascularization, even in the presence of electrocardiographic Q waves.

Pathophysiologically, myocardial viability refers to those cardiomyocytes that are alive, defined by a presence of cellular, metabolic, and microscopic contractile function. On the other hand, in a clinical setting, viability is defined by the presence of dysfunctional myocardium at rest with a potential for functional recovery on restoration of normal blood supply. Currently, hibernation and stunning are the general subdivisions of viable myocardium with different but overlapping characteristics. The concept of hibernation was originally thought to be an adaptive process by which the myocardium downregulates its contractile function in the presence of sustained reduced blood flow. Subsequently, experimental studies in animals have highlighted the continuum between episodes of repetitive ischemia, stunned myocardium (contractile dysfunction with normal resting flow), and hibernating myocardium. In a swine model of progressive coronary stenosis, stunned myocardium preceded the development of hibernating myocardium,[5,6] suggesting that reduced resting flow in hibernating myocardium may be a result rather than a cause of contractile dysfunction. Myocardial stunning refers to a state of decreased contractile function caused by transient episodes of hypoperfusion. During repetitive stunning, cardiomyocytes undergo structural changes, with loss of their contractile apparatus, sarcoplasmic reticulum, and t tubules and increased glycogen plaques.[7] These changes eventually become irreversible (Figure 1).[8] Whether resting blood flow is normal or reduced, coronary flow reserve (CFR) is decreased,

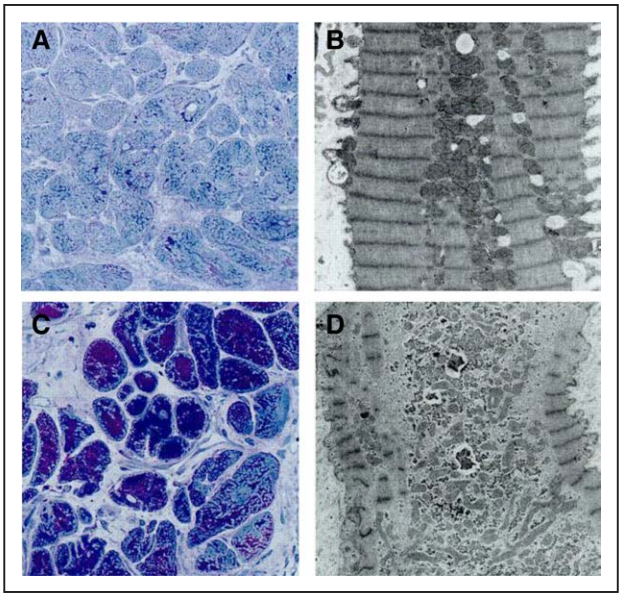

Figure 1. Histological changes in the hibernating myocardium. **A**, Light micrograph of myocardium showing normal cardiomyocytes with virtually no glycogen (periodic acid–Schiff [PAS] staining in red). **B**, Transmission electron micrograph of normal cardiac myocyte. **C**, Representative light micrograph of biopsy sample of human hibernating myocardium. Cardiac myocytes are depleted of their contractile material and filled with glycogen (PAS-positive staining). **D**, Representative transmission electron micrograph of a hibernating cardiomyocyte. Myolytic cytoplasm is devoid of sarcomeres and filled with glycogen. Modified from Vanoverschelde et al.[8] Copyright © 1997, American Heart Association, Inc.

leading to repetitive episodes of demand ischemia, impaired calcium handling, and reduced sarcoplasmic reticulum sensitivity to calcium.[9]

Viability imaging has significant clinical implications. Identifying dysfunctional myocardium that has a potential for restoration of contractile function can inform decisions on invasive coronary revascularization. Conversely, the extent of myocardial scar is associated with left ventricular (LV) remodeling and increased risk of sudden cardiac death.[10] Furthermore, hibernating myocardium also creates a substrate for ventricular tachyarrhythmias.[11]

MOLECULAR AND HISTOLOGICAL IMAGING

The transition from viable myocardium to necrosis entails fundamental metabolic and histologic changes that include, among others, metabolic adaptation, gene expression, loss of mitochondrial function, apoptosis, and expansion of extracellular space. Advanced cardiovascular imaging techniques have been and currently are being developed to assess these pathophysiological phenomena, which are interrogable pathways and surrogates of myocardial viability.

Under resting physiological conditions, the myocardium uses beta oxidation of fatty acids as its substrate given its increased ATP yield relative to glucose.

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However, when oxygen deprivation occurs, myocardial metabolism will transition to glucose oxidation given its more efficient ATP production during ischemic states.[12] In this setting, glucose transporter 1 is upregulated, thereby facilitating glucose entry into the myocardium. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) detects this metabolic switch by demonstrating increased tracer uptake in viable tissue. Additional PET metabolic tracers that may aid in the assessment of myocardial metabolism and its relation to viability include ^{11}C-palmitate, which assesses fatty acid metabolism, and ^{11}C-acetate, which may be used to quantify myocardial oxygen consumption.[13]

Myocardial tissue sampling has demonstrated the upregulation of tumor necrosis factor-α and nitric oxide synthase in hibernating myocardium. Greater mRNA expression of these cardio-inhibitory cytokines has been postulated to contribute to depressed myocardial contractility.[14] Ischemia-provoked acidosis results in the opening of the mitochondrial permeability transition pore, causing a loss of the mitochondrial membrane potential. Consequently, the mitochondrial membrane ruptures, releasing cytochrome C, which triggers a cascade of events, ultimately resulting in apoptosis. Animal models have demonstrated the ability to measure the mitochondrial membrane potential by radiolabeled tetraphenylphosphonium.[13]

Several radionuclide isotopes have been developed to assess for apoptosis and ultimately necrosis that occur once the mitochondrial membrane ruptures, including technetium-99m (99mTc)–pyrophosphate, indium-111 (^{111}In)-antimyoain, and 99mTc–annexin V. Specifically, 99mTc-annexin V can detect caspase-induced irregularities of membrane phospholipid distribution.[15]

Once necrosis has occurred, myocardial cell contents escape into the interstitium, thereby increasing the extracellular space and inducing an inflammatory reaction. Necrosis from an MI can also leave an expanded extracellular space where an intravenously administered gadolinium contrast will accumulate. Cardiovascular magnetic resonance (CMR) imaging can detect this increased extracellular space with T1-weighted late gadolinium enhancement (LGE) imaging because regions of myocardial fibrosis present as areas of high-intensity signal in contrast to surrounding nulled myocardium.[16]

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IMAGING IN THE CLINICAL SETTING

Invasive Coronary Angiography

Coronary angiography and intravascular imaging tools can assess anatomy and function of coronary arteries and myocardium and play an important role in the evaluation of myocardial viability. The presence of a high-grade proximal stenosis, distal TIMI (Thrombolysis in Myocardial Infarction) grade III flow, myocardial blush of contrast, and collateral blood flow all suggest viable myocardium.[17] Improved myocardial contractility after administration of intravenous nitroglycerine or inotropic stimulation with low-dose dobutamine also suggests myocardial viability.[18]

Compared with viable myocardium, basal and hyperemic myocardial blood flow is reduced in infarcted myocardium as a result of microvascular dysfunction and smaller myocardial mass. Invasively, coronary pressure and velocity can be measured during pharmacologically induced hyperemia. Adenosine-induced fractional flow reserve (FFR) is affected not only by stenosis severity but also by the amount of viable myocardium supplied by that artery and collateral perfusion. This means that the FFR value distal to a stenosis would be lower when viable myocardium is present compared with when nonviable (infarcted) myocardium is present. In patients with chronic MI, lower FFR before revascularization and improvement in FFR after revascularization are predictive of myocardial recovery. One study suggested the cutoff value of 0.70 for FFR to discriminate patients who may have improved myocardial function.[19] In the acute ST-segment–elevation MI setting, however, the accuracy of FFR in the infarct-related artery is affected by significant microvascular derangement (stunning); therefore, FFR is not reliable. Recently developed adenosine-free indexes of assessment of epicardial artery such as instantaneous wave-free ratio and resting ratio of distal to proximal pressure appear promising but have not been validated for assessment of myocardial viability.

The integrity of the coronary microvasculature is an important determinant of myocardial viability. Compared with irreversibly damaged myocardium, viable myocardium has been shown to have normal microvascular resistance, and the degree of microvascular damage after acute MI is an important predictor of myocardial recovery after revascularization.[20] Invasive measurement of coronary blood flow velocity is the gold standard method for the assessment of microvascular function. Based on invasive measurement of resting and hyperemic pressure and flow, various indexes of microvascular resistance exist, including CFR, index of microcirculatory resistance, and hyperemic microvascular resistance. CFR measured in the infarct-related artery after percutaneous coronary intervention predicts recovery of LV function after ST-segment–elevation MI.[21] Although CFR is affected by the presence of epicardial disease and hemodynamic perturbations, indexes of pure microvascular function such as the index of microcirculatory resistance and hyperemic microvascular resistance are more specific for the assessment of viability in this setting.[22] Measured after revascularization in patients with acute MI, the index of microcirculatory resistance is predictive of myocardial viability in the early recovery phase and LV wall motion recovery

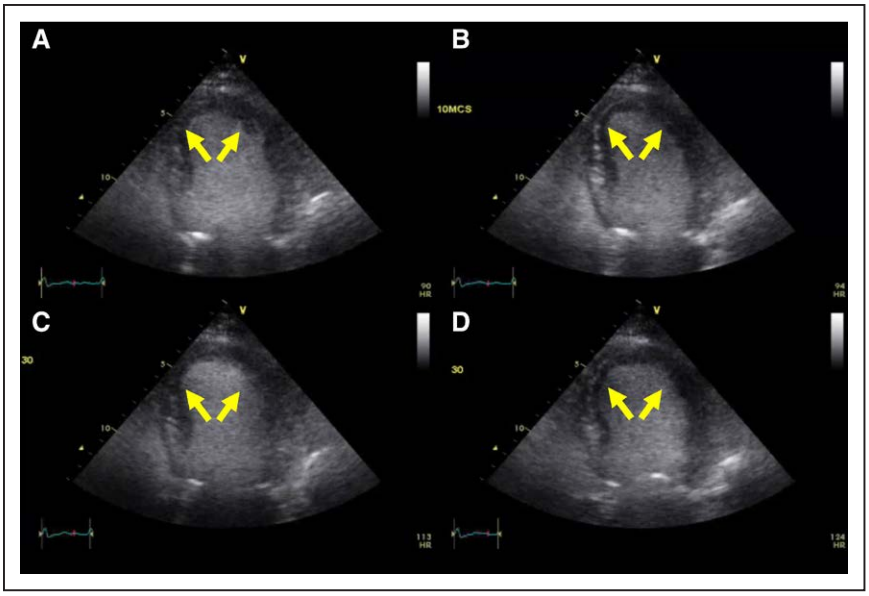

Figure 2. Contrast-enhanced dobutamine echocardiography.
Example showing end-systolic images obtained at rest (**A**) and with low-dose (**B**) and high-dose (**C** and **D**) dobutamine showing a biphasic response in the left anterior descending artery territory (arrows).

at 6 months,[23] and it correlates with other noninvasive measures of LV function. In patients with chronic MI, improvement in CFR after revascularization predicts myocardial functional recovery. Therefore, simultaneous measurement of FFR and CFR has been proposed to improve the predictive significance of invasive assessment in these patients.[19] Finally, myocardial blush grade, TIMI grade, and TIMI frame count are simple, albeit less accurate, measurements of coronary microvascular function that can be assessed by angiography.

Echocardiography

Assessment of resting LV size and function is fundamental to the evaluation of myocardial viability. LV wall thinning and increased echo backscatter are thought to be markers for scarring. An LV end-diastolic wall thickness (EDWT) of <6 mm was initially reported to practically exclude relevant amount of viable myocardium.[24] However, this result was more recently challenged by Shah et al,[25] who showed that about one-fifth of segments with regional wall thinning caused by ischemic heart disease without evidence of LGE demonstrate LV function improvement after revascularization with reversal of wall thinning. Increased LV end-systolic volume is associated with worse clinical outcomes after revascularization.[26] In patients with LV end-systolic volume >130 mL, a marker for extensive LV remodeling, cardiac events were 38% higher after 3 years after revascularization, despite metabolic evidence of "viable" myocardium.

Dobutamine stress echocardiography is a readily available imaging tool to assess myocardial viability and contractile reserve. When a segment of regional wall does not contract at rest, low-dose dobutamine (2.5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) can be infused to increase contractility in a viable myocardium. Continuation of graded dobutamine

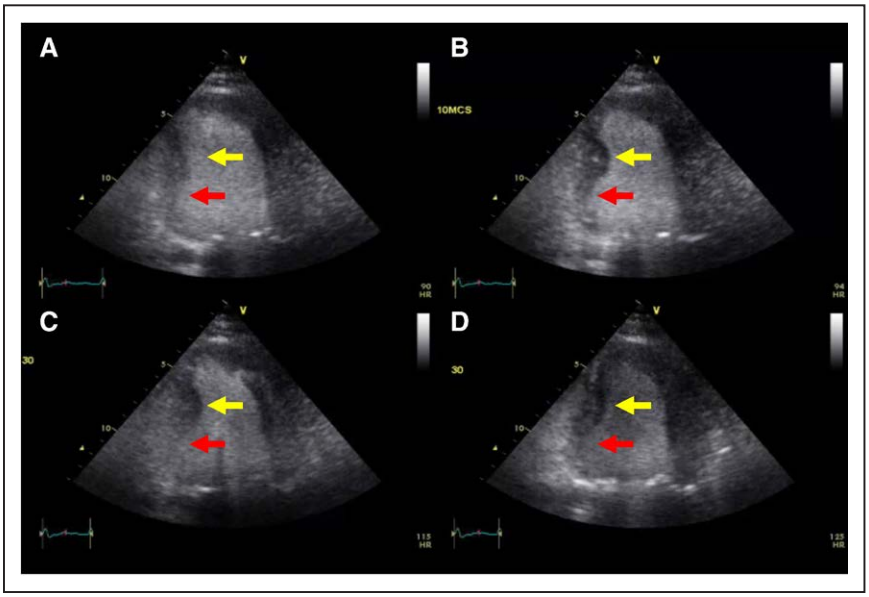

Figure 3. Contrast-enhanced dobutamine echocardiography.
Example showing end-systolic images obtained at rest (**A**) and with low-dose (**B**) and high-dose (**C** and **D**) dobutamine showing a biphasic response in the midinferior wall (yellow arrows) and a scar at the basal inferior wall (red arrows) in the same patient.

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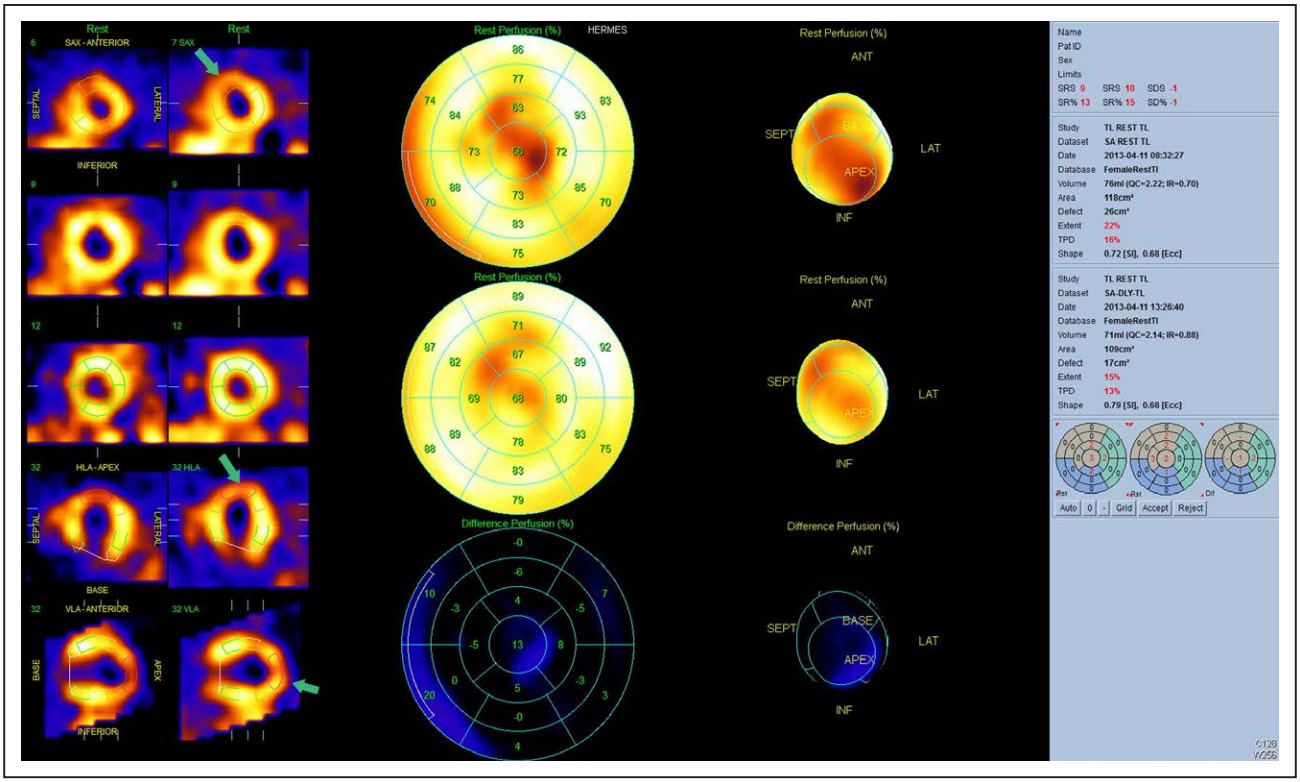

Figure 4. Rest and 24-hour redistribution single-photon emission computed tomography (SPECT) thallium-201 (^{201}Tl) study.
A rest (**left** column, **top** bullet plot) and 24-hour redistribution (**right** column, **bottom** bullet plot) SPECT ^{201}Tl study demonstrates increased tracer uptake in the anterior (ANT), septal (SEPT), and apical segments after 24 hours (arrows), consistent with viable myocardium in this territory. HLA indicates horizontal long axis; INF, inferior; LAT, lateral; SAX, short axis; and VLA, vertical long axis.

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infusion (10–40 μg·kg^{-1}·min^{-1}) may lead to either further improvement in contractility or diminished wall motion (Figures 2 and 3). The latter is known as a biphasic response to dobutamine, which is predictive of recovery of myocardial function after revascularization, with diagnostic sensitivity and specificity of 76% and 81%, respectively.[27] This phenomenon represents an initial increase in regional coronary flow with improved myocardial perfusion and contractility, followed by an inability to escalate blood flow to myocardium to match oxygen demand during higher-dose dobutamine challenge. Sustained improvement in myocardial contractility during graded infusion also demonstrates ischemic viable myocardium but may be a normal response in nonischemic dilated cardiomyopathy.

Detecting cardiac microvascular integrity is essential in the assessment of myocardial viability in akinetic segments. Echo contrast perfusion volume and velocity to the myocardium depend on the amount and speed of tissue capillary blood flow. Resting myocardial blood flow, as quantified by replenishment of echo contrast agent after high mechanical index pulse destruction of gas-filled microbubbles, can effectively distinguish viable and nonviable myocardium.[28] This technique appears to be highly sensitive but less specific for the detection of viability compared with dobutamine stress echocardiography. When these 2 modalities are harmonized, diagnostic accuracy may be improved. However, echo contrast perfusion imaging is highly dependent on technical expertise with high reported interobserver and intraobserver variabilities, and its use for viability assessment currently remains off-label.[29]

Tissue Doppler imaging and speckle tracking echocardiography to assess myocardial deformation have demonstrated promising roles in the evaluation of viable myocardium. Conceptually, speckle tracking echocardiography is more sensitive in detecting viability in ischemic cardiomyopathy because mechanical changes involving the subendocardium may be more readily identified during dobutamine stress echocardiography compared with qualitative visual assessment. Speckle tracking echocardiography with its ability to perform layer-specific analysis has been shown to predict LV functional recovery and remodeling after acute MI. In a preliminary study, its diagnostic accuracy was reported to be similar to that of LGE-CMR.[30]

Nuclear Scintigraphy

Single-photon emission computed tomography (SPECT) and PET radioisotopes that are capable of measuring blood flow and myocardial metabolism have been used to identify the presence of myocardial viability.

Introduced in the 1970s, thallium-201 (^{201}Tl) is a potassium analog that is actively transported across the myocardial cell membrane via Na^+/K^+ ATPase-dependent channels. In contrast to nonviable myocardial tissue, viable

myocytes will have an intact cell membrane and associated transport mechanism and therefore will demonstrate ^{201}Tl uptake. Furthermore, viable myocardial tissue may not initially demonstrate ^{201}Tl uptake but may do so on delayed an imaging, a characteristic defined as redistribution.

Several ^{201}Tl viability protocols have been developed. Rest-redistribution protocols entail a rest image followed by an additional redistribution image 4 hours later with an increased tracer uptake of ≥10% in areas with a resting defect suggestive of viability. Stress-redistribution protocols call for ^{201}Tl stress imaging followed by 4-hour redistribution imaging. However, the accuracy of this protocol was limited, calling for further refinement with the addition of either late redistribution (18–24 hours) imaging (Figure 4) or a small reinjection dose of ^{201}Tl after the 4-hour redistribution images. Both techniques were similar in their ability to detect viable myocardium with a positive predictive value of 69% and negative predictive value of 89%.[31] Further advancements in ^{201}Tl viability imaging include quantification of radiotracer uptake when a continuous relationship between uptake and likelihood of improved myocardial contractility after revascularization has been demonstrated.[32]

^{99m}Tc-based agents, including the lipophilic cationic compound sestamibi and the diphosphine agent tetrofosmin, were introduced several decades after ^{201}Tl. Unlike ^{201}Tl, ^{99m}Tc-based agents passively diffuse across the cell membrane, where their uptake and retention depend on the maintenance of an electrochemical gradient across mitochondrial and sarcolemma membranes, and they do not demonstrate redistribution properties.

Imaging protocols using these radiotracers include rest-stress protocols and rest protocols with nitrate enhancement.[33] Although both ^{201}Tl and ^{99m}Tc-sestamibi are considered class I agents with similar accuracy for detecting viability,[34] technetium-based agents have more favorable imaging characteristics because of higher photon energy and less radiation exposure.

Several new isotopes are currently being investigated, including ^{99m}Tc-nitrido complexes such as DBODC5 and mitochondrial complex-1 inhibitors such as ^{123}I-CMICE-013, both of which have demonstrated excellent target-to-background ratios.[35] Further human studies are needed.

PET imaging for viability involves a combination of rest myocardial perfusion imaging (MPI) and metabolic imaging with ^{18}F-FDG.[36] PET agents for rest MPI include N-13

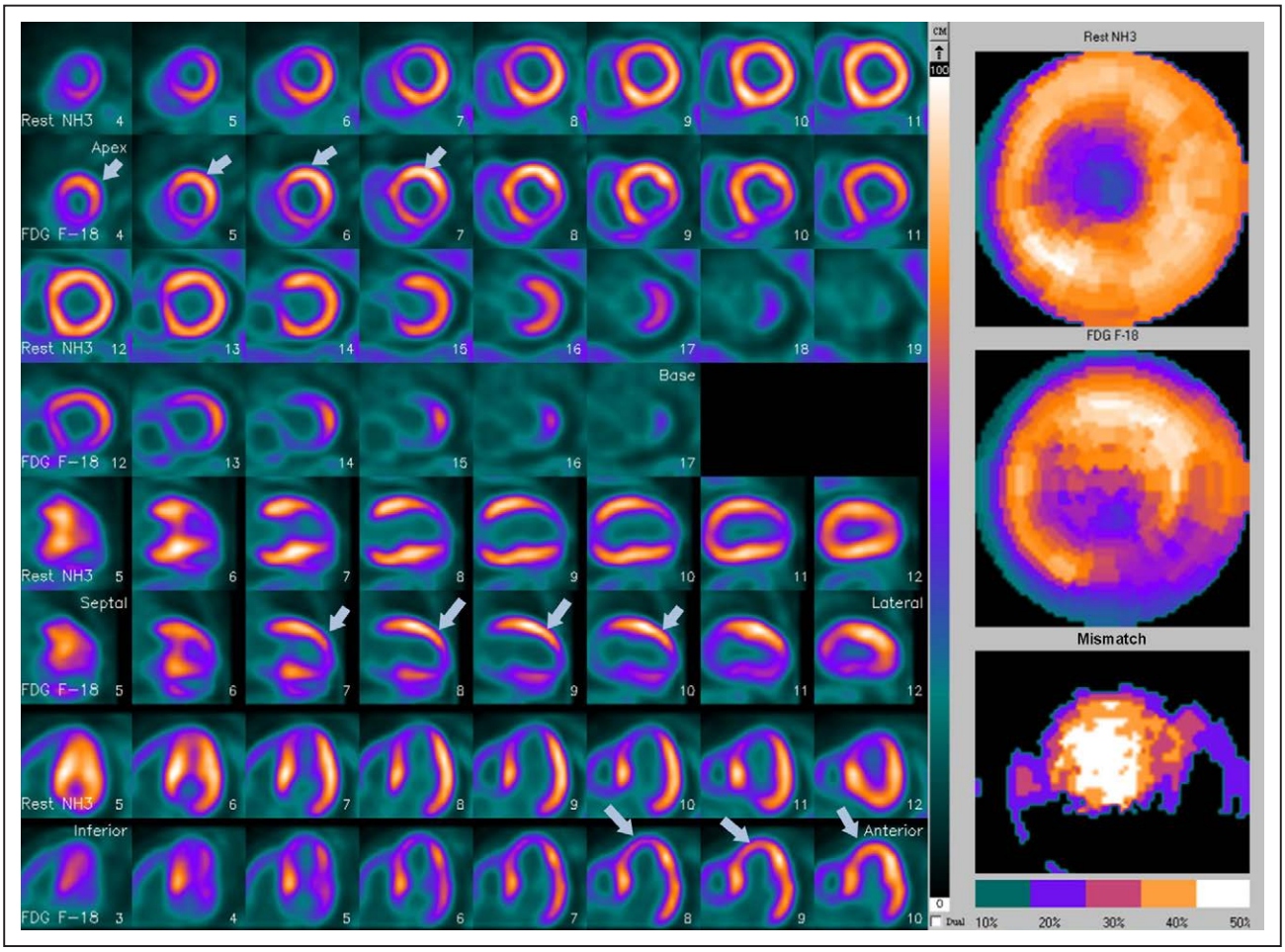

Figure 5. Dual-isotope positron emission tomography viability study.
Example showing large area of viability in the distribution of the left anterior descending artery (reduced NH_3 with preserved fluorodeoxyglucose [^{18}F-FDG] uptake, arrows). Courtesy of Mark Travin, MD, Montefiore Medical Center.

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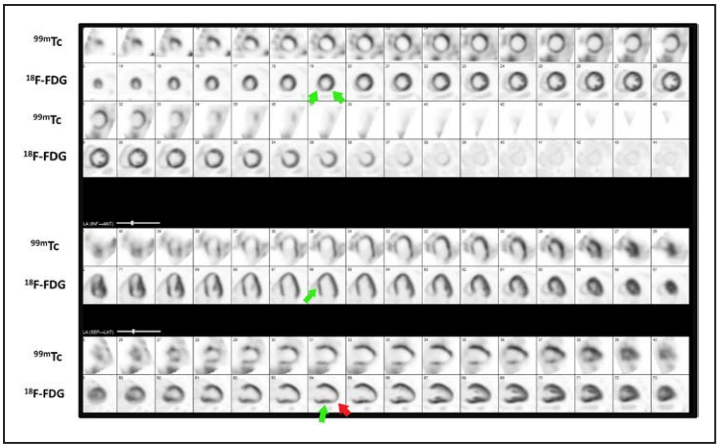

Figure 6. Dual-isotope single-photon emission computed tomography viability study.
A 70-year-old man with prior coronary artery bypass graft surgery and new left ventricular systolic dysfunction. Fluorodeoxyglucose (^{18}F-FDG) images demonstrate a significant amount of viable myocardium (mismatch pattern) in the distribution of the septal perforators and the right coronary artery (green arrows), except for a small amount of scar (matched reduction in flow and ^{18}F-FDG uptake) involving the distal apical inferior wall (red arrows). ^{99m}TC indicates technetium-99m.

ammonia and rubidium-82 (^{82}Rb). In addition, ^{18}F-labeled perfusion agents are under investigation, and ^{15}O-labeled water agents are clinically used in Europe but are not yet approved by the US Food and Drug Administration. Compared with SPECT MPI, the advantages of PET MPI include improved spatial resolution, better attenuation correction, and lower radiation dose. These advantages are highly relevant in viability images because they allow better identification of the presence, extent, and severity of scar. It is also possible to combine SPECT MPI with ^{18}F-FDG PET metabolic imaging.

A PET viability study relies on first obtaining rest MPI images. In the absence of perfusion defects, there is no need to proceed with metabolic images. However, an evaluation for ischemia may be helpful if there is uncertainty about whether the severity or burden of coronary artery disease (CAD) results in ischemia. When such uncertainty exists, a quantitative evaluation of myocardial blood flow at stress in addition to rest may be helpful because retrospective data have shown that the presence of abnormal myocardial blood flow reserve may identify patients who are more likely to derive benefit from coronary revascularization.[37] However, the accuracy and utility of quantitative assessment of myocardial blood flow have not been adequately tested in patients with low ejection fraction (EF) or prior coronary artery bypass graft surgery (CABG).

In areas that lack resting perfusion, preserved glucose metabolism, identified via uptake of ^{18}F-FDG, is a marker of myocardial viability. In contrast, the absence of glucose metabolism indicates nonviable myocardium (Figure 5). The assessment of ^{18}F-FDG uptake requires careful patient preparation in order to promote glucose metabolism by the myocardium. This is achieved by loading the patient with glucose (usually an oral load

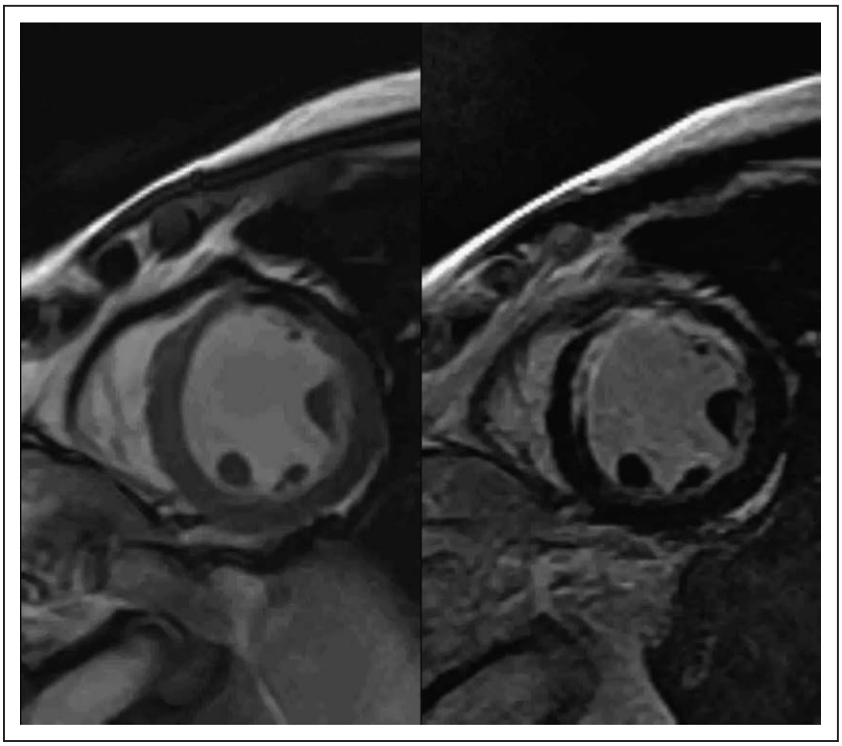

Figure 7. Cardiovascular magnetic resonance imaging of a patient with a chronic anterior infarction.
Left, Thinned and akinetic segments are noted in the anterior and anteroseptal walls. In these thinned and akinetic anterior segments, infarction was transmural. **Right**, Late gadolinium enhancement imaging demonstrating ≈50% transmural extent of infarction in the anterolateral and anteroseptal segments.

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of 25–50 g) after a fasting period of at least 6 hours, thereby inducing endogenous insulin release. In addition, insulin may be administered to increase glucose metabolism. Recent advances in technology also allow high-resolution metabolic imaging to be performed with SPECT cameras (Figure 6).

In the evaluation of rest MPI and ^{18}F-FDG PET images, there are 3 patterns to recognize: (1) hibernating myocardium, that is, reduced myocardial perfusion with preserved ^{18}F-FDG uptake; (2) transmural scar, which is absent myocardial perfusion with absent ^{18}F-FDG uptake; and (3) nontransmural scar, which is partially reduced myocardial perfusion with concordant ^{18}F-FDG uptake. Although a post hoc analysis of the PARR-2 trial (PET and Recovery Following Revascularization-2) suggests that the larger the areas of mismatch are (ie, extent of viable myocardium), the greater the potential benefit of revascularization is with respect to clinical outcomes,[38] this has not been a consistent finding. The overall results of this study, as discussed later, failed to demonstrate survival benefits related to viability testing.

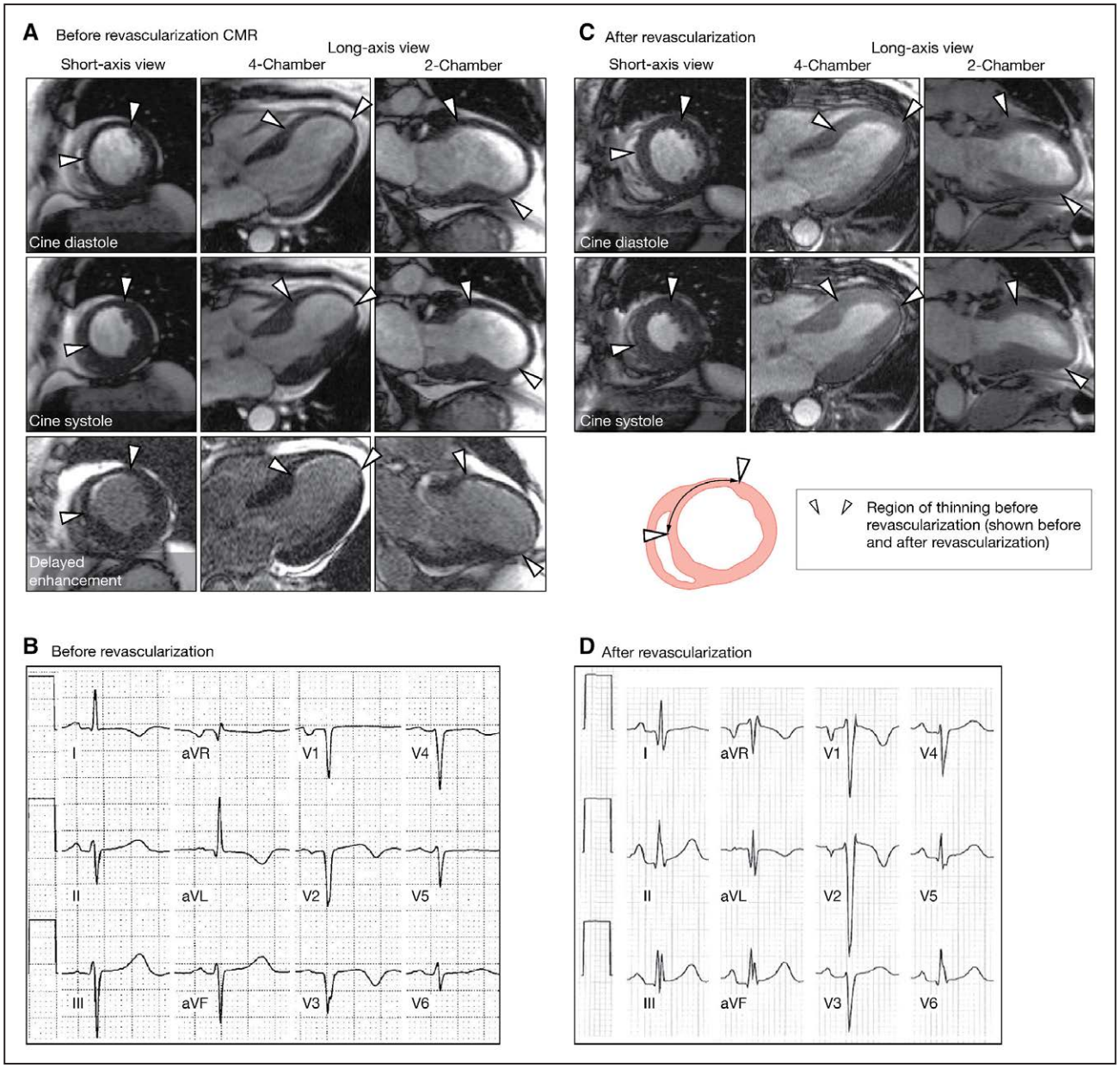

Figure 8. Cardiovascular magnetic resonance (CMR) imaging and electrocardiographic changes in an example of a patient with wall thinning and limited scar burden.

Arrows demarcate the edges of the subendocardial myocardial infarction. In this case, the anterior left ventricle was noted to be thinned and akinetic, with evidence of a subendocardial myocardial infarction that spanned <50% of the transmural extent. As predicted by the <50% transmural extent of infarction, the thinned segments recovered contractile function after coronary revascularization. **A**, Cardiac magnetic resonance before revascularization. **B**, Cardiac magnetic resonance after revascularization. **C**, Electrocardiogram before revascularization. **D**, Electrocardiogram after revascularization. Reproduced from Shah et al[25] with permission. Copyright © 2013, American Medical Association. All rights reserved.

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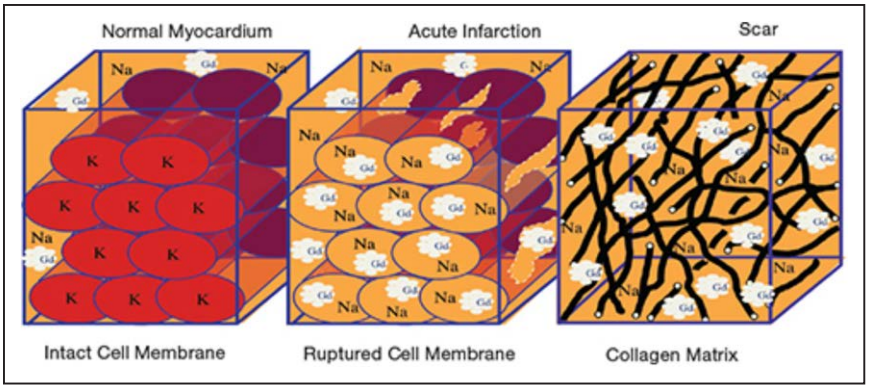

Figure 9. Potential mechanisms of late gadolinium enhancement (LGE).
In the short- and long-term settings, LGE is believed to result directly from an absence of viable myocytes. Resultant increases in gadolinium extracellular volume of distribution produce T1 shortening, which manifests as signal enhancement on LGE imaging. Modified from Weinsaft et al[41] with permission from Elsevier. Copyright © 2007, Elsevier.

CMR Imaging

CMR characterizes suspected hibernating myocardium by a combination of techniques: LV EDWT, inotropic reserve of segmental contractile function, and transmural extent of MI with LGE imaging (Figure 7). Other CMR methods, including quantification of segmental contractile reserve with feature tracking or myocardial tagging or magnetic resonance spectroscopy for assessment of high-energy phosphates metabolism (eg, quantification of concentration and ratio of ATP and phosphocreatine with P-31 spectroscopy within a small volume of myocardium), are not in routine clinical use and are not covered here.

In patients with chronic CAD, wall thinning most often develops as a result of infarct resorption and fibrotic contracture, but it may also occur as a result of severe ischemia. Thus, EDWT alone has limited prediction for functional recovery after revascularization. Baer et al[39] reported that an EDWT cutoff of 5.5 mm had a 94% sensitivity but only 52% specificity for predicting segmental functional recovery after revascularization. The low specificity of LV wall thinning can be attributed to the fact that EDWT as a structural variable does not assess physiological response of the myocardium and that there is a wide variation of EDWT between individuals and even between different myocardial segments in the same individual.[40] As Shah et al[25] demonstrated, ≈20% of dysfunctional and thinned myocardial segments have limited scar burden; indeed, they are viable by demonstrating improved contractility and resolution of wall thinning after coronary revascularization (Figure 8).

Gadolinium-based contrast agents (GBCAs) shorten the T1 relaxation time of the surrounding tissues proportional to the local gadolinium concentration. In normal state, gadolinium, which is a large, high-density element made metabolically inert by chelation, enters the extracellular space readily after intravascular injection, but it is unable to cross the cell membrane of a normal myocyte. However, when the myocyte cell membrane is damaged (eg, acute MI) or if there is an increase in the extracellular space between myocytes (eg, acute interstitial edema or chronic fibrosis or MI), GBCA accumulates in the extracellular space, and its washout is delayed after the injection (Figure 9).[41] Thus, areas of abnormal myocardium (eg, infarcted, fibrotic, inflamed, or infiltrated myocardium) will have elevated per-voxel GBCA concentration and therefore will have a bright signal on T1-weighted images relative to the surrounding normal myocardium. In clinical CMR, the most common current protocols use a GBCA at 0.1 mmol/kg patient weight and then perform LGE imaging at 10 minutes after GBCA injection. However, with the latest GBCAs, LGE imaging as early as 5 minutes has been reported to be reliable and successful.[42] In LGE imaging, the signal from normal myocardium is suppressed (nulled) by an inversion recovery preparation pulse.[43] When LGE imaging is used in patients with CAD, dysfunctional myocardium with normal nulled signal intensity suggests myocardial stunning or hibernation and an absence of infarction. In chronic MI, the LGE characteristically involves the subendocardium or progresses to involve the entire transmural extent in myocardial segments subtended by a coronary arterial territory. In patients with chronic CAD with LV dysfunction being evaluated for benefits of coronary revascularization, the transmural extent of the LGE provides a prediction of the stepwise decreasing likelihood of improvement in segmental myocardial contractility after coronary revascularization (Figure 10).[44] Akinetic segments with no or minimal subendocardial infarction have a >90% chance of segmental recovery of contractile function if the involved coronary artery is successfully revascularized. Those segments with > 50% transmural extent of infarction have a <10% chance of segmental contractile recovery despite successful coronary revascularization. In segments that demonstrate <50% transmural extent of infarction, functional recovery is not well predicted by the criteria using LGE transmural extent alone, and it can benefit from assessment by inotropic contractile reserve. The major advantage of contrast-enhanced CMR is the ability to assess the presence of subendocardial MI and to delineate the transmural extent of MI at high spatial resolution (typically 1–3 mm in-plane resolution) and contrast-to-noise ratio in characterizing myocardial tissues.[45] The common bright-blood LGE method can sometimes be challenging in detecting the presence and extent of some subendocardial MI because of suboptimal contrast

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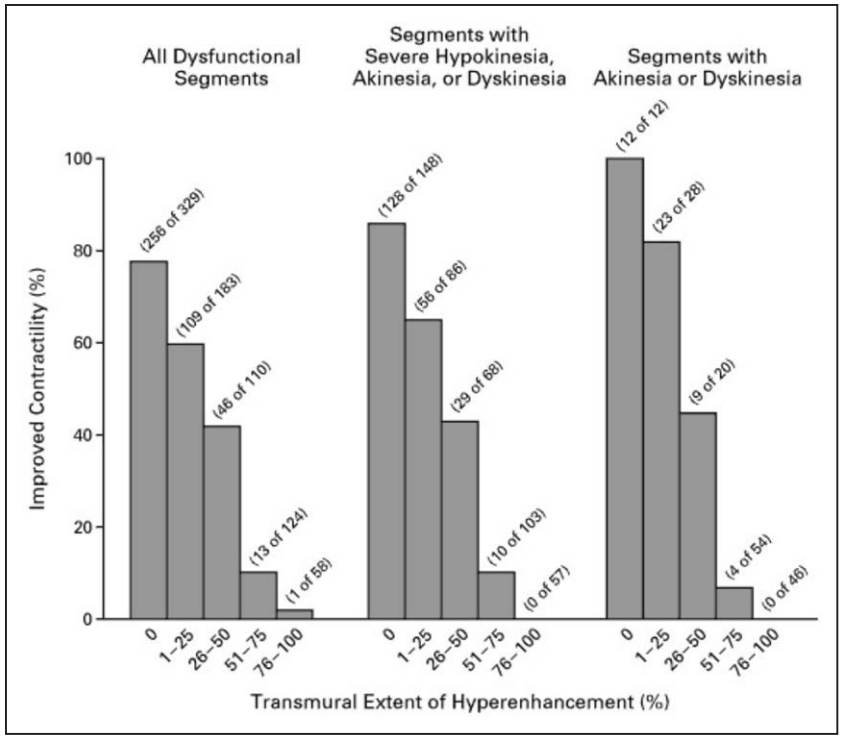

Figure 10. Stepwise likelihood of contractile recovery of segment function stratified by transmural extent of late gadolinium enhancement (LGE).
The transmural extent of LGE was significantly related to the likelihood of improvement in contractility after revascularization. When all segments that were dysfunctional before revascularization were analyzed, the proportion with improved contractility decreased progressively as the transmural extent of LGE increased. Reproduced from Kim et al[44] with permission from Massachusetts Medical Society. Copyright © 2000, Massachusetts Medical Society.

between blood and MI, especially early after contrast injection. Dark-blood imaging using T2 or other preparations to achieve dark-blood pool effect to improve the visualization of subendocardial MI are increasingly being used, especially in experienced centers.[46]

Inotropic contractile reserve in response to low-dose dobutamine infusion (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is a well-validated physiological assessment of myocardial viability by either echocardiography or CMR.[47,48] Compared with other methods, inotropic contractile reserve tends to achieve a higher specificity because it examines a similar end point of segmental contractile function but a lower sensitivity. Schmidt et al[49] compared the prediction of segmental functional recovery between resting EDWT, dobutamine induced wall thickening, and ^{18}F-FDG PET in patients with chronic MI. The sensitivity and specificity were 100% and 53% for resting EDWT ≥5.5mm alone, 96% and 87% for dobutamine-induced contractile reserve of 2 mm, and 100% and 73% for preserved ^{18}F-FDG (>50%) uptake.[49] Dichotomizing using a threshold value of resting EDWT or ^{18}F-FDG uptake is less accurate than the physiological assessment using low-dose dobutamine challenge. Wellnhofer et al[48] also demonstrated that dobutamine-induced contractile reserve has a higher specificity than the transmural extent of LGE imaging to predict segmental functional recovery, especially with 1% to 74% transmural extent of late enhancement. On the other hand, it should be noted that although inotropic contractile reserve is specific, it is only moderately sensitive in the prediction of segmental contractile recovery.[50] Reduced sensitivity of dobutamine CMR can be attributed to the development of ischemia even at low-dose dobutamine in segments subtended by a tight coronary stenosis or long-term depletion of contractile filaments in hibernating myocardium. A prolonged infusion of low-dose dobutamine may allow the building up of inotropic effects and the resultant display of augmentation of segmental thickening, enhancing the sensitivity for detecting segmental viability. A meta-analysis of 24 published CMR studies argues that the combination of these techniques may improve the overall accuracy of viability assessment. In this compendium, LGE provided the highest sensitivity of 95% in predicting segmental functional recovery after revascularization, which was complemented by a high specificity of 91% offered by dobutamine contractile reserve.[51]

Cardiac Computed Tomography

The concept of myocardial hyperenhancement to index extracellular volume expansion by imaging began with computed tomography (CT).[52,53] Several differences characterize hyperenhancement defined by contrast-enhanced CT as opposed to CMR. The fundamental difference between the CMR and CT methods is that in CT the contrast agent molecule directly informs extracellular volume size by express interference with the x-ray beam, whereas in CMR, the effect is indirect by shortening the relaxation time of water hydrogen atoms sensitized by proximity with the GBCA molecule. Another difference between the 2 methods that carries clinical significance is the smaller molecular size

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Table. Sensitivity, Specificity, and Positive and Negative Predictive Values of Noninvasive Imaging Predicting Improvement of Regional Function After Revascularization

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

Db-CMR indicates dobutamine cardiovascular magnetic resonance; Db-Echo, dobutamine echocardiography; LGE-CMR, late gadolinium-enhanced cardiovascular magnetic resonance; PET-^{18}F-FDG, positron emission tomography–fluorodeoxyglucose; NPV, negative-predictive value; PPV, positive predictive value; ^{99m}Tc, technetium-99m; and ^{201}Tl, thallium-201.

Data derived from Romero et al[51] and Schinkel et al.[57]

of iodine-based contrast agents compared with the GBCAs used in CMR. This leads to a shorter time for optimal imaging by CT, ≈5 minutes, as opposed to 10 to 15 minutes by CMR.

The development of multirow detector CT created novel opportunities for CT delayed enhancement as a modality to image replacement fibrosis and thus index myocardial viability.[54] Greater spatial resolution and tissue coverage provided by multirow detector CT translated into improved tissue characterization with accurate delineation of myocardial necrosis with preserved microvascular structure versus inner infarct areas, reflecting microvascular obstruction secondary to early endothelial necrosis and microvascular collapse caused by profound prolonged ischemia at the center of myocardial infarcts. These myocardial tissue patterns defined by contrast-enhanced CT were validated against contrast-enhanced CMR and histopathology.[55] However, the lower contrast-to-noise ratio of CT compared with LGE-CMR is an important limitation of this method as a clinical tool. The ability to obtain more precise iodine mapping with the recently introduced multienergy CT systems may potentially overcome this limitation, but this requires more extensive validation.

MODALITY COMPARATIVE STUDIES

Imaging modalities and methods evaluate different sequelae of stunning and hibernation, including abnormal myocardial blood flow, metabolism, contractile reserve, and extracellular volume. The alterations observed in these physiological parameters vary according to the magnitude and duration of ischemia, loading conditions, and myocardial remodeling.[56] The Table[51,57] provides a summary of the performance characteristics of various imaging modalities for the detection of functional recovery. Differences in study design, including timing of patient enrollment relative to last ischemic event, mode, and extent of follow-up after revascularization, all contribute to a variable incidence of segmental function recovery. Advances in medical therapy, revascularization, and strategies for preventing sudden cardiac death have also evolved over time. Hence, comparing performance characteristics of viability imaging tests from different cohorts is rather difficult. Pooled data from 3034 patients enrolled in 105 studies demonstrated similar degrees of accuracy for SPECT, PET, and dobutamine echocardiography, with relatively higher sensitivity for PET ^{82}Rb-^{18}F-FDG and ^{201}Tl rest-redistribution and higher specificity for dobutamine echocardiography.[58] A subanalysis of 15 studies that conducted a head-to-head comparison between SPECT and PET yielded similar results.[57] Nevertheless, the presence of viability is associated with a similar degree of improvement in LVEF after revascularization (8%–10%), regardless of whether radionuclide-based imaging or dobutamine echocardiography is used.[59] To achieve significant improvement in global systolic function, it appears that 25% to 30% of myocardial segments must exhibit dysfunction and viability.[60] The performance characteristics of CMR vary according to whether the variable studied is the presence of contractile reserve with dobutamine, EDWT, or percentage of LGE. Compared with SPECT, PET, and dobutamine echocardiography, LGE >50% of wall thickness on CMR has a higher negative predictive value for segmental recovery with a positive predictive value comparable to that of radionuclide-based methods, whereas presence of contractile reserve on dobutamine CMR has the highest positive predictive value but lowest negative predictive value (Table).

CLINICAL SCENARIOS

The following represent some of the common clinical scenarios in which viability assessment may be helpful in clinical decision-making. It is important to highlight that the benefit of revascularization should always be assessed in the context of other factors,

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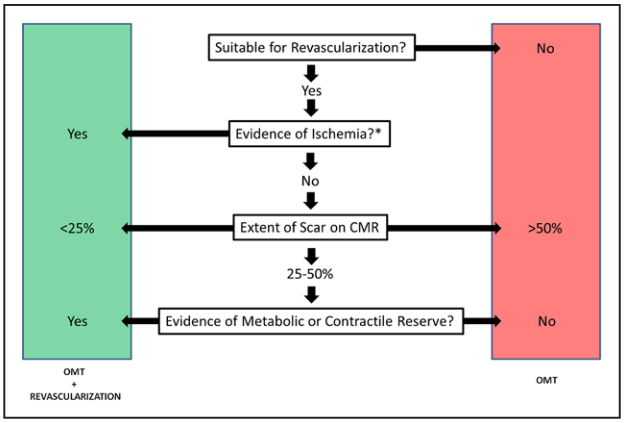

Figure 11. Algorithm for the evaluation of patients with chronic ischemic left ventricular dysfunction.
CMR indicates cardiovascular magnetic resonance; and OMT, optimal medical therapy. *Defined by anginal symptoms, electrocardiographic monitoring, or imaging testing.

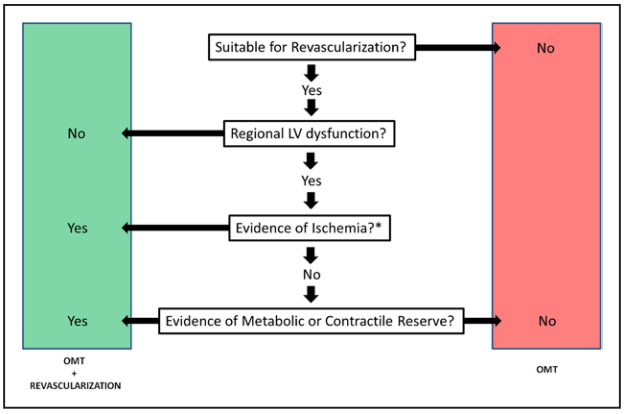

Figure 12. Algorithm for the evaluation of patients with subacute ischemic left ventricular (LV) dysfunction.
OMT indicates optimal medical therapy. *Defined by anginal symptoms, electrocardiographic monitoring, or imaging testing.

including the probability of achieving successful revascularization and the severity of adverse remodeling.[61] Figures 11 and 12, although not clinically validated, are proposed by consensus of the authors of this document.

Case 1

A 38-year-old man with a history of familial dyslipidemia and cigarette smoking was evaluated for symptoms of dyspnea and leg edema, progressing over several months. On examination, he had findings consistent with decompensated heart failure. His ECG showed abnormal Q waves in V_1 through V_3. Transthoracic echocardiography (TTE) demonstrated mild LV dilatation with anteroapical hypokinesis and an EF of 35%. A coronary angiogram showed 75% stenosis of the proximal LAD. CMR showed evidence of LGE in the LAD territory with 25% to 50% transmural thickness. ^{201}Tl rest-redistribution showed a small fixed perfusion defect at the apex (Figure 13). The patient underwent percutaneous coronary intervention with a drug-eluting stent. A follow-up TTE obtained 3 months later showed apical hypokinesis and an LVEF of 50%. The workup of this patient follows Figure 11. He had sustained development of HF symptoms caused by ischemia/repetitive stunning. His initial TTE shows regional hypokinesis in the LAD territory with preserved LV wall thickness. A decision to perform viability testing was made in the absence of anginal symptoms after coronary angiography showed occlusive CAD suitable for revascularization. CMR showed a scar of 25% to 50% transmurality, suggesting an intermediate probability of functional recovery. ^{201}Tl rest-redistribution, however, demonstrated intact metabolic activity in the LAD territory with the exception of a small apical segment.

Case 2

A 72-year-old woman with hypertension, type 2 diabetes mellitus, and chronic kidney disease presented to the emergency department with dyspnea worsening over 24 hours. She described an episode of chest

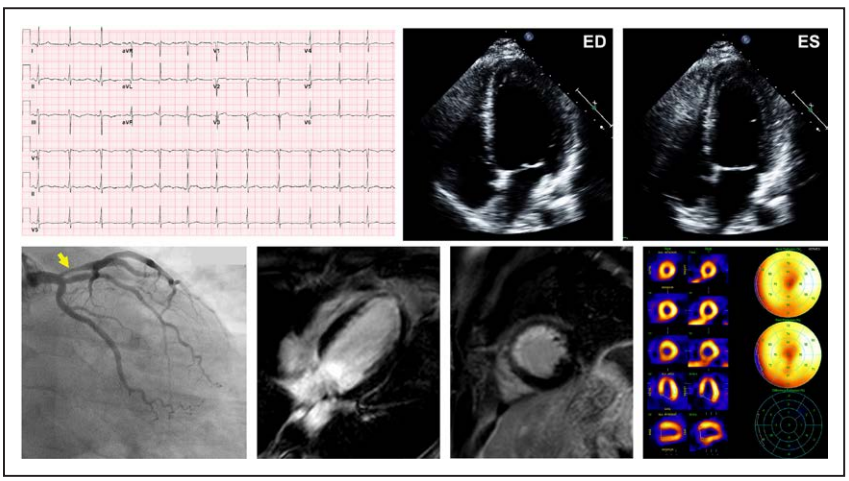

Figure 13. Case 1 imaging testing findings (see text for details).
ED indicates end-diastolic frame; and ES, end-systolic frame.

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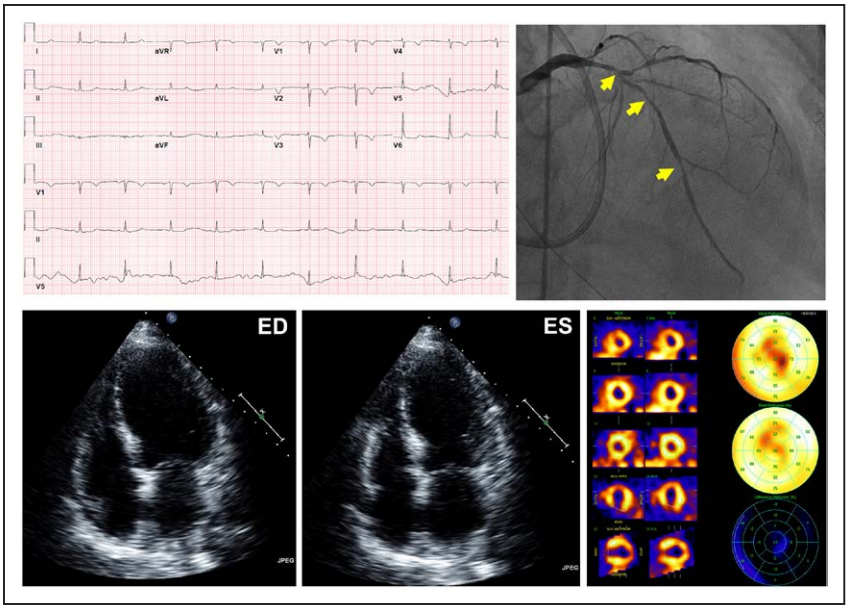

Figure 14. Case 2 imaging testing findings (see text for details).
ED indicates end-diastolic frame; and ES, end-systolic frame.

and epigastric discomfort after dinner 2 nights before that she attributed to indigestion. Her physical examination demonstrated an S_3 gallop and bilateral inspiratory rales. Her ECG showed inverted T waves in the precordial leads. At the emergency department, her serum troponin T was 2.5 ng/mL (normal, <0.04 ng/mL) and creatine phosphokinase was 180 IU/L (normal range, <192 IU/L). TTE showed anteroapical akinesis and an EF of 40%. A coronary angiogram showed several obstructive lesions in the mid and distal LAD and in the first and second diagonal branches. ^{201}Tl rest-redistribution showed a moderate anteroapical perfusion defect at rest that decreased in size after 24 hours (Figure 14). The patient was referred for CABG surgery. The workup of this patient follows Figure 12. She presented with acute decompensated heart failure after a recent ischemic event. Her history and cardiac enzyme pattern indicated that she experienced an MI >24 hours before her presentation to the emergency department. Her angiogram demonstrated obstructive CAD in the LAD territory, corresponding to the TTE findings. The complexity of her CAD increases her risk for periprocedural complications. The evidence of viability on her ^{201}Tl rest-redistribution study indicating stunned but viable LAD territory provides a justification against the risks of revascularization.

Case 3

A 78-year-old woman with a history of hypertension was admitted to the hospital with acute decompensated heart failure. She reported symptoms starting as a flu-like illness about a week before. Her ECG on admission showed sinus tachycardia, left anterior fascicular block, abnormal Q waves, and 1-mm ST-segment elevation in anterior precordial leads. Her cardiac enzymes were normal but serum creatinine was 2.2 mg/dL (normal, <1.3 mg/dL). TTE showed anteroseptal akinesis and an EF of 30%. A coronary angiogram showed several obstructive lesions in the distal LAD and a diagonal branch. ^{201}Tl rest-redistribution showed a large anteroapical perfusion defect at rest with minimal improvement after redistribution (Figure 15). The patient was recommended optimal medical therapy. The workup of this patient also follows Figure 12. She presented with acute decompensated heart failure. Her history suggested that she experienced a recent MI. Her angiogram demonstrated obstructive CAD in the LAD territory, corresponding to the TTE findings. She had coronary anatomy consistent with her wall motion abnormality on TTE, but she was also at high risk for periprocedural complications because of her complex coronary anatomy and kidney disease. The lack of viability on her ^{201}Tl rest-redistribution study indicating scar on the LAD does not provide a justification against the risks of revascularization.

LESSONS FROM RECENT CLINICAL TRIALS

Whether improvement in LV systolic function after revascularization, as predicted by preprocedural assessment of myocardial viability, results in improved clinical outcomes has been the subject of intense interest. The 10-year results of the multicenter randomized STICH trial (Surgical Treatment for Ischemic Heart Failure) demonstrated improved long-term all-cause and cardiovascular mortality with surgical revascularization of patients with ischemic cardiomyopathy (LVEF ≤35%) compared with patients receiving guideline-directed medical therapy (GDMT).[62] However, this late survival

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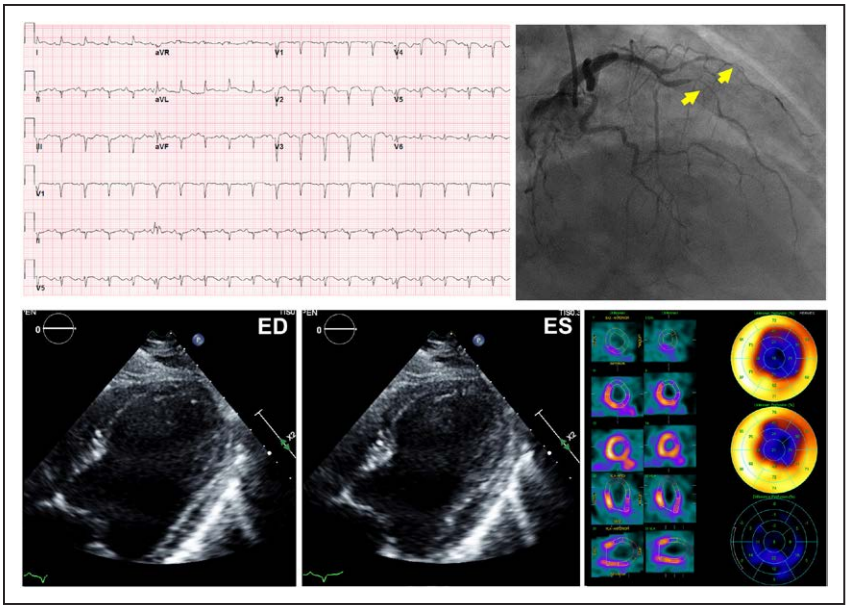

Figure 15. Case 3 imaging testing findings (see text for details).
ED indicates end-diastolic frame; and ES, end-systolic frame.

benefit was achieved at the expense of higher short-term 30-day mortality after CABG, which highlights the importance of appropriate patient selection for CABG.

To determine whether viability testing is helpful in identifying patients most likely to benefit from revascularization, a prespecified viability substudy of STICH assessed baseline myocardial viability with SPECT imaging or dobutamine echocardiography in 618 of the 1212 enrolled STICH patients.[57] The substudy defined myocardial viability by prespecified binary thresholds determined in prior studies but performed additional analyses using continuous viability scores.[38] Patients with myocardial viability had lower 5-year mortality rate (33% versus 50%), but viability status by these methods did not discriminate patients who would derive a mortality benefit from CABG plus GDMT compared with GDMT alone. Similar findings were observed for the secondary end points of cardiovascular mortality or combined mortality and cardiovascular hospitalization. These results run counter to previous retrospective data summarized in meta-analysis and systematic reviews[25,59] that reported improved survival with revascularization compared with medical therapy in patients with viable but dysfunctional myocardium. The STICH results may be explained by the greater adherence to GDMT, particularly β-adrenergic blockers, which were not used as frequently, if at all, in earlier studies. The latest results of the STICH viability substudy continue to demonstrate no significant interaction between the presence or absence of myocardial viability and the beneficial effect of CABG plus GDMT over GDMT alone.[63] Although an increase in LVEF was observed only among patients with myocardial viability, the increase was similar in magnitude in patients treated with GDMT and those treated with CABG. Finally, survival was not related to whether LVEF increased; 10-year survival was 64% in those with an increase in LVEF and 62% in those with no improvement in LVEF. These findings are not unique in that they support the observations of Samady et al[64] 20 years earlier that survival after CABG in patients with LV systolic dysfunction (mean EF, 24%) did not depend on whether EF increased postoperatively.

PET has been suggested to assess myocardial viability more precisely than SPECT. However, in the PARR-2 trial, patients randomized to PET viability imaging did not demonstrate improved survival after CABG compared with standard care.[65] Moreover, in the meta-analysis of Orlandini et al,[61] PET assessment of viable myocardium was not superior to SPECT or dobutamine echocardiography in predicting survival after revascularization in patients with LV dysfunction.

After STICH and PARR-2, whether myocardial viability imaging can assume any role in making critical decisions about CABG in patients with CAD and severe LV dysfunction has been questioned. STICH and PARR-2 represent the most significant efforts to date to address the roles of SPECT and dobutamine echocardiography and of PET, respectively, in the management of patients with CAD and LV dysfunction. However, neither study could model all the key factors involved that determine patient survival. Their results reflect the complexities in decision-making for patients with severe CAD and LV dysfunction being considered for surgical coronary revascularization, with numerous clinical risk markers and clinician discretion at play that affected patient outcomes, beyond an imaging assessment of myocardial viability. Modern medical therapies have also advanced substantially and reduced the incremental survival benefit of CABG over medical therapy. Future prospective trials should not only use innovative designs with adequate study power to adjust for multiple interactive clinical factors

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but also incorporate different quantitative measurements to fully capture the spectrum of myocardial viability. Perhaps most important, future trials should focus on patients in whom the management decision to proceed with CABG is truly difficult because of age, comorbidities, and other factors, and the additional information from viability imaging could indeed affect treatment decisions and thus perhaps improve patient survival.

FUTURE DIRECTIONS

Although there is a lack of evidence to support that viability testing leads to improved survival in patients with ischemic heart disease, we believe that it plays an important role in clinical decision-making in many of these patients for the following reasons. (1) Patients with ischemic cardiomyopathy and LV dysfunction are at high risk for cardiovascular events. (2) Myocardial revascularization may provide benefits to selected high-risk patients with multivessel CAD and LV dysfunction. (3) Functional recovery after revascularization is more likely to be observed in myocardial segments that demonstrate viability, regardless of the imaging modality used. Clearly, management decisions in patients with ischemic cardiomyopathy are complex and require integrating other factors such as the anatomic substrate, patient comorbidities, and risk. Currently available imaging methods evaluate different aspects of myocardial physiology and for that reason may yield at times conflicting but at other times complementary results. It is increasingly recognized that any single imaging test that expresses myocardial viability in a dichotomized fashion will unlikely fully characterize the physiological complexity of both the ischemic myocardium and coronary revascularization.[63] Furthermore, the use of restoration of regional or global LV contractile function has been tasked as the clinical gold standard, but it has been known to insufficiently characterize patient benefits in this setting.[64] Accordingly, future trials should continue to address the clinical impact of specific modality-based strategies or multimodality strategies in guiding treatment in terms of patient outcomes. On the other hand, appropriately guided coronary revascularization may go beyond providing recovery of myocardial systolic contractility by improving patient's functional class and heart failure symptoms, enhancing diastolic relaxation, reducing the burden of rhythm abnormalities, or decreasing the burden of polypharmacy, thereby reducing the risk of drug toxicity and improving quality of life. These additional benefits need also to be explored in clinical trials.

ARTICLE INFORMATION

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Disclosures

Writing Group Disclosures

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*Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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Warren J. Manning	Harvard University, Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None
Michael H. Picard	Massachusetts General Hospital	NHLBI (research support, collaborator)†; Actelion (support for core lab services [no direct compensation])†; Philips Healthcare (research support [no direct compensation])*	None	None	None	None	None	None

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