REVIEW

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Myocardial Perfusion and Viability Imaging in Coronary Artery Disease: Clinical Value in Diagnosis, Prognosis, and Therapeutic Guidance

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ABSTRACT

Coronary artery disease is a leading cause of morbidity and mortality worldwide. Noninvasive imaging tests play a significant role in diagnosing coronary artery disease, as well as risk stratification and guidance for revascularization. Myocardial perfusion imaging, including single photon emission computed tomography and positron emission tomography, has been widely employed. In this review, we will review test accuracy and clinical significance of these methods for diagnosing and managing coronary artery disease. We will further discuss the comparative usefulness of other noninvasive tests—stress echocardiography, coronary computed tomography angiography, and cardiac magnetic resonance imaging—in the evaluation of ischemia and myocardial viability.

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KEYWORDS: Coronary artery disease; Coronary computed tomography angiography; Myocardial ischemia; Myocardial perfusion imaging; Myocardial viability; Positron emission tomography; Single photon emission computed tomography

INTRODUCTION

Coronary artery disease is a leading cause of mortality and morbidity worldwide.[1] Although coronary angiography remains the "gold standard" for diagnosing the presence and severity of coronary artery disease, various noninvasive imaging tests offer high sensitivity and specificity for diagnosis and risk stratification and provide guidance for revascularization. In this article, we will 1) review the clinical usefulness of myocardial perfusion imaging, single photon emission computed tomography and positron emission tomography, for the evaluation of coronary artery disease and myocardial viability; 2) compare the scintigraphic methods to other noninvasive tests, including stress echocardiography, coronary computed tomography angiography, and cardiac magnetic resonance imaging; and 3) demonstrate the role of imaging in evaluating myocardial viability.

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MYOCARDIAL PERFUSION IMAGING

General Principles

Myocardial perfusion imaging reflects relative differences in the distribution of blood flow in the myocardium at rest and during stress, which may be produced by exercise or by pharmacological means. Myocardial arterioles distal to a significant epicardial coronary stenosis are dilated by autoregulation to maintain myocardial blood flow at rest. Stress conditions cause significant vasodilation of normal vascular beds, but little additional dilation in vascular beds distal to significant coronary stenoses, leading to differences in perfusion, appearing as "defects" in myocardial perfusion images. This original method has been supplemented by images that demonstrate ventricular function.

Standard displays of the poststress and rest images are demonstrated and compared in transverse (short axis), vertical long axis and horizontal long axis (Figure 1A).

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Perfusion defects are described by a standardized 17-segment model of the left ventricle (Figure 1B). An irreversible (fixed) defect (ie, seen on both at rest and stress images) indicates infarction, whereas a perfusion defect seen after stress but reversible (not seen) on resting images indicates myocardial ischemia (Figure 1B). Figure 1C demonstrates correlative angiographic findings.

Exercise is the preferred stress method because it provides valuable prognostic information.[2] Pharmacological stress is indicated for 1) patients who are unable to achieve adequate exercise[3] and 2) patients with left bundle branch block or ventricular pacing, which often show relative septal hypoperfusion accentuated by exercise and can be mistakenly interpreted as ischemia.[4] Pharmacological stress tests (regadenoson is most commonly used at present) have similar sensitivity and specificity compared to exercise stress testing.[5]

CLINICAL SIGNIFICANCE

- Single photon emission computed tomography has extensive prognostic data for coronary artery disease.
- Positron emission tomography offers higher accuracy over conventional scintigraphy.
- Scintigraphic imaging demonstrates physiological significance while coronary computed tomography primarily detects anatomic stenosis.
- Myocardial viability tests reveal the likelihood of functional improvement following revascularization.
- The choice of the best test depends on facility resources and individual patient characteristics.

Pitfalls in Study Interpretation

First, myocardial perfusion imaging may underestimate the presence of 3-vessel or left main disease due to "balanced perfusion defects" during stress.[6,7] The additional findings of transient ischemic left ventricular dilatation and reduced left ventricular ejection fraction during stress improve the diagnostic sensitivity in these scenarios.[6,7] Second, disorders other than epicardial coronary disease may produce false-positive findings in patients with nonischemic, dilated cardiomyopathy.[8,9] Importantly, coronary microvascular disease[10] can be associated with perfusion abnormalities. Third, attenuation artifact from the soft tissue can affect study accuracy, although the effect can be reduced by attenuation correction software. Attenuation from an elevated diaphragm can cause an apparent inferior defect, whereas persistent breast attenuation may simulate anterior infarction.[11,12] Lateral wall defects may be observed in women and patients who are obese.[12]

Single Photon Emission Computed Tomography for Diagnosis and Prognosis in Coronary Artery Disease

^{99m}Tc-based radiopharmaceuticals have largely replaced ^{201}Tl because of improved dosimetry, better spatial imaging resolution, and less soft-tissue attenuation,[11] leading to greater test accuracy.[13] The sensitivity and specificity of ^{99m}Tc perfusion imaging are reported 68%-74% and 71%-79%, respectively[14,15] (Table 1). In studies of good quality, the sensitivity and specificity of visually assessed exercise stress ^{99m}Tc imaging are 73%-96% and 70%-89%, respectively.[5]

Decades of experience with single photon scintigraphy has contributed to abundant data, demonstrating its prognostic role. In a study of 5183 patients, the annual risks of cardiac death and myocardial infarction were 0.3% and 0.5%, respectively, in 2946 patients with normal perfusion images, in contrast to 6% and 9.8%, respectively, in 2237 patients with abnormal images.[19] In patients with known coronary artery disease, the physiological information obtained by myocardial perfusion imaging improves risk stratification beyond the anatomical information of coronary angiography.[16]

Positron Emission Tomography for Diagnosis of Coronary Artery Disease

These images are of better quality than single photon computed tomographic images due to better resolution and attenuation correction,[17] leading to a greater accuracy in localizing disease to individual coronary arteries.[20] Importantly, positron emission tomography can quantify myocardial blood flow and myocardial flow reserve, which significantly enhances the diagnosis of coronary artery disease.[20] The sensitivity and specificity of positron emission imaging was reported 84% and 87%, respectively, in a meta-analysis[15] (Table 1).

Other Methods for Diagnosis of Coronary Artery Disease

Coronary computed tomography angiography, stress echocardiography, and cardiac magnetic resonance imaging are all useful for the diagnosis of coronary artery disease. Table 1 displays the results of selected, high-quality meta-analyses. The most significant advantages and disadvantages, plus sensitivity and specificity of these methods, are summarized.

Coronary Computed Tomography Angiography. The main advantage of coronary tomography angiography is the anatomical detection of coronary lesions with high sensitivity. On the other hand, its specificity is relatively low, largely due to blooming effects from heavy coronary calcification.[14,15,21] Therefore, this method has been more commonly used in younger patients with low to intermediate risk. Recent techniques, including stress perfusion and calculated coronary fractional flow reserve, increase the overall test specificity to 87% and 85%, respectively,[22,23] compared to 54% by computed tomography angiography

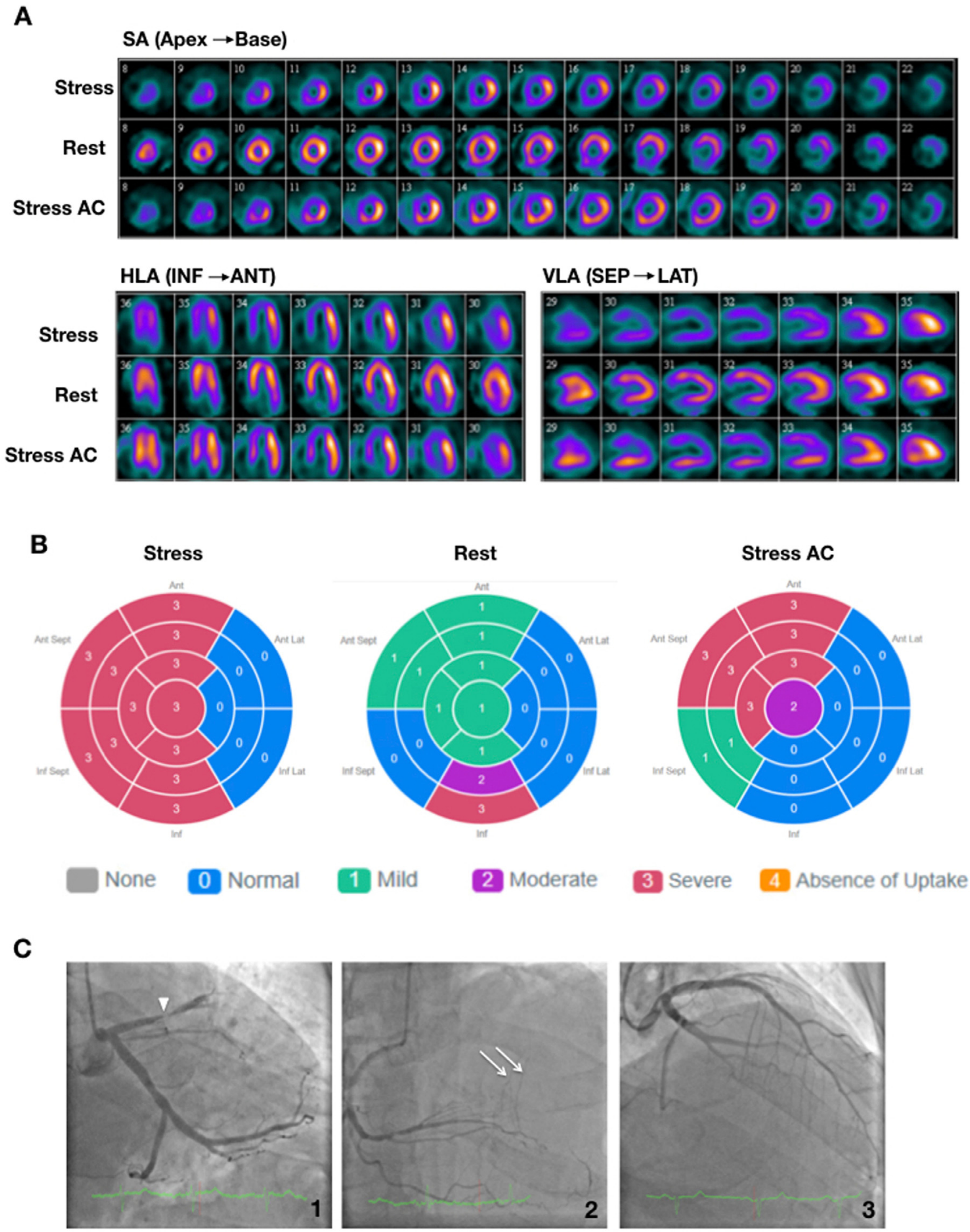

Figure 1 An example of myocardial perfusion imaging in correlation with coronary angiogram. **(A)** Perfusion scan showing anterior and septal ischemia. **(B)** A 17-segment model corresponding to perfusion imaging. (Severity denoted by numbers and colors.) Moderate-severe reduction of activity on poststress image, mostly reversible on rest image is consistent with ischemia. Mild reduction in activity at rest is due to prior nontransmural infarction. Poststress attenuation corrected image demonstrates that apparent inferior defect on poststress image is largely due to diaphragmatic attenuation. **(C)** Coronary angiogram demonstrates: 1) Focal 95% stenosis of proximal left anterior descending artery (arrowhead); 2) insignificant lesion of right coronary artery that sends collateral vessels to LAD (arrows); 3) widely patent anterior descending artery following stent placement. AC = attenuation correction; ANT = anterior; HLA = horizontal long axis; INF = inferior; LAT = lateral; SA = short axis; SEP = septal; VLA = vertical long axis.

Table 1 Comparison of Noninvasive Tests (at Patient Level) for Diagnosing Coronary Artery Disease

Test	Sensitivity	Specificity	Advantages	Disadvantages
SPECT	0.68-0.74[16,17]	0.71-0.79[16,17]	1) Inexpensive, and widely available 2) Associated with prognosis	1) Radiation exposure 2) Higher false-negativity for multivessel disease 3) Higher false-positivity due to attenuation
PET	0.84[17]	0.87[17]	1) Greater accuracy than SPECT 2) Improved diagnosis of multivessel disease 3) Anatomical information 4) Associated with prognosis	1) Limited by availability and expertise of facility 2) Radiation exposure
Stress echo	0.39-0.77[16,17]	0.75-0.93[16,17]	1) No radiation or contrast exposure 2) Structural information 3) Higher specificity in female and obese patients	1) Dependence on technical and imaging quality as well as reader experience 2) Lower sensitivity for diagnosing single vessel coronary artery disease
Coronary CT angiogram	0.90-0.94[16,18] CTP[28]: 0.83 FFT_{CT}[28]: 0.89	0.39-0.48[16,18] CTP[28]: 0.79 FFR_{CT}[28]: 0.76	1) Anatomical details including plaque characteristics 2) High sensitivity; also detects atherosclerosis without critical stenosis	1) Radiation & contrast exposure 2) Relatively low specificity improved with CT-FFR_{CT} or CTP 3) Affected by calcium-related artifacts
Cardiac MRI	0.89-0.90[16,17]	0.87-0.94[16,17]	1) High sensitivity and specificity 2) Detailed structural information	1) Expensive and not universally available 2) Contraindicated in advanced renal disease 3) Affected by arrhythmia, tachycardia and breath-holding skills

CT = computed tomography; CTP = (coronary) computed tomography perfusion; FFR = (coronary) fractional flow reserve; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.

The sensitivity and specificity data are obtained from multiple meta-analyses (see reference), with invasive serving as gold standard. The analyses were performed at patient level to determine the test accuracy in ischemia detection, without localization to a specific vessel.

alone[22] (Table 1). The coronary fractional flow reserve by computed tomography angiography has better performance than positron emission imaging in identifying vessel-specific lesions;[24] but on a per-patient level, the specificity is lower.[24]

The current North American guidelines favor noninvasive functional imaging over coronary computed tomography angiography as a first-line diagnostic tool for most patients with suspected myocardial ischemia.[25] However, the 2016 guideline from the National Institute for Health and Care Excellence (NICE) in the United Kingdom favors coronary computed tomography angiography as the first test in patients without known coronary artery disease.[26] A meta-analysis of randomized clinical trials comparing coronary computed tomography angiography to other imaging methods showed that former was associated with a lower incidence of subsequent myocardial infarction.[27] This may be due to detection of nonobstructive disease that prompted more aggressive medical therapy and increased referral for angiography and revascularization.[27] The disadvantages of computed tomography angiography include radiation and contrast exposure, the lack of physiological exercise data, and greater expense than myocardial perfusion imaging. This process can increase the number of subsequent cardiac catheterizations[28] and the "downstream costs."[18]

This controversy will continue, with more results to follow. The overarching issue will be deciding the best strategy for treating stable coronary artery disease as outlined in recent publications from the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial.[29,30] This controversy highlights the evolution in the choice of diagnostic test from aiming at the "best accuracy" to the "best outcome."

Stress Echocardiography. Similar to perfusion scanning, stress echocardiography, either with exercise or dobutamine stimulation, is commonly employed for evaluating myocardial ischemia by producing ischemic wall motion abnormalities.[31] The sensitivity of stress echocardiography is lower than ^{99m}Tc perfusion imaging, but specificity is greater.[14,15] This is likely owing to a greater extent of ischemia needed to produce a wall motion abnormality than needed to produce a perfusion abnormality.[14,15] On the other hand, stress echocardiography has greater specificity than ^{99m}Tc perfusion imaging in females and patients with left ventricular hypertrophy.[32]

Stress Cardiac Magnetic Resonance Imaging. Magnetic resonance imaging may employ pharmacological vasodilation or dobutamine, each with similar sensitivity and specificity for diagnosing coronary artery disease.[33,34] The sensitivity and specificity of stress cardiac magnetic resonance imaging with myocardial perfusion are 89%-90% and 87%-94%, respectively, in meta-analyses.[14,15] Dobutamine is more often employed when gadolinium is contraindicated. In randomized trials, the sensitivity of stress magnetic resonance imaging was greater than perfusion imaging, but the specificity of perfusion imaging was greater.[35-38] There are several important limitations of cardiac magnetic resonance imaging, including a lack of information about exercise capacity, contraindication in patients with incompatible cardiovascular implantable electronic devices, relatively limited availability of devices, and imaging expertise compared to other methods.

Limitations of Analyses. Myocardial ischemia may be due to both epicardial obstructive coronary artery disease and microvascular dysfunction.[10] All tests that are based on physiology demonstrate the summed effects of macrovascular and microvascular causes of ischemia. Thus, they are valuable in this regard but also will not solely reflect epicardial coronary artery disease.

The extensive literature regarding sensitivity, specificity, and other measures of test validity is subject to potential errors.[39,40] In addition, the field of analyzing the value of a specific test is evolving toward outcomes evaluation, rather than simply establishing a diagnosis of coronary artery disease. Here, we will discuss the value of scintigraphic imaging and other imaging modalities in predicting revascularization outcomes for patients with ischemic cardiomyopathy.

EVALUATION OF MYOCARDIAL VIABILITY

Myocardial stunning and hibernation were defined in 1970s and 1980s. "Myocardial stunning" is the condition of myocardial contractile dysfunction after brief ischemia followed by the relief of ischemia, without irreversible tissue damage.[41] In contrast, "myocardial hibernation" refers to the condition of chronic contractile dysfunction in the setting of persistent hypoperfusion, with the potential for improved contractility after revascularization.[42,43] Both stunned and hibernating myocardium are considered viable.

Revascularization in patients with ischemic cardiomyopathy can reduce long-term mortality.[44-46] However, cardiac performance improves in some but, not all, patients.[47] Selection of the patients with ischemic and viable myocardium who will benefit from revascularization has been the goal of myocardial viability studies. Hibernating or stunned myocardium can be detected by multiple imaging modalities, including scintigraphic imaging, dobutamine stress echocardiography, and cardiac magnetic resonance imaging.

Single Photon Emission Computed Tomography

Both ^{201}Tl and ^{99m}Tc-based imaging has been studied, but ^{201}Tl has been more commonly employed for detecting hibernating myocardium.[48] Bonow et al[48] showed generally good correlation for detecting viable myocardium between ^{201}Tl imaging and ^{18}F-flurodeoxyglucose positron emission tomography imaging. However, with severe, irreversible ^{201}Tl defects, positron imaging was superior.[48]

Positron Emission Tomography for Assessing Myocardial Viability

Metabolic imaging with ^{18}F-fluorodeoxyglucose reflects myocardial glucose uptake, consistent with viability and has the highest sensitivity among the viability tests[49] (Table 2). A comprehensive meta-analysis of pooled studies[49] showed a sensitivity and specificity in predicting segmental wall motion improvement after revascularization of 87% and 54% by ^{201}TI-based protocols and 92% and 63% for ^{18}F-fluorodeoxyglucose positron emission tomography[49] (Table 2). It is preferred in facilities with this technology and experience.

Four principal patterns of perfusion and metabolism may be observed on perfusion and metabolism images[51]

Table 2 Comparison of Myocardial Viability Tests for Predicting Recovery of Contractility Following Coronary Revascularization[50]

Test	Studies (*N*)	Patients (*N*)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
^{201}Tl SPECT	40	1119	87	54	67	79
^{99m}Tc SPECT	25	721	83	65	74	76
PET	24	756	92	63	74	87
DSE	41	1421	80	78	75	83
Dobutamine CMR	9	272	74	82	78	78
CMR with gadolinium	5	178	84	63	72	78

CMR = cardiac magnetic resonance; DSE = dobutamine stress echocardiography; NPV = negative predictive value; PET = positron emission tomography; PPV = positive predictive value; SPECT = single photon emission computed tomography.
Data are summarized from the meta-analysis by Schinkel et al.[50]

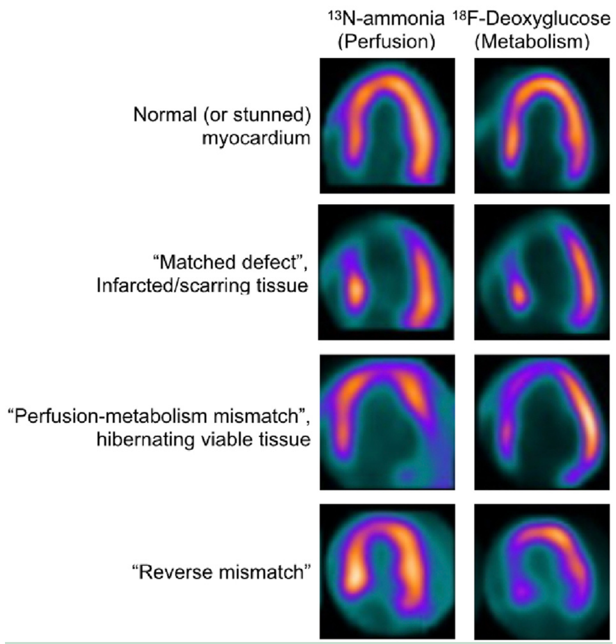

Figure 2 Patterns of myocardial viability on positron emission tomographic images.

(Figure 2). 1) Normal perfusion and metabolism suggest normal myocardium or ischemic stunning in the setting of reduced contractility; 2) reduced perfusion with preserved metabolism (perfusion-metabolism mismatch) suggests hibernating myocardium; 3) the combination of reduced perfusion and metabolism (matched defects) indicates nonviable, infarcted myocardium; and 4) rarely, a "reverse mismatch pattern" is found where normal perfusion coexists with reduced metabolism. This has been observed early after revascularization[52] and reflects a shift of metabolic substrate to free fatty acids.[53] Other rare instances have also been reported.[50,54]

Other Methods: Dobutamine Stress Echocardiography and Cardiac Magnetic Resonance Imaging

Dobutamine stress echocardiography and dobutamine stress cardiac magnetic resonance imaging examine myocardial contractile reserve. An improvement of wall motion in hypokinetic/akinetic regions with low-dose dobutamine followed by deterioration with higher-dose dobutamine signifies hibernating myocardium. These tests predict functional recovery after revascularization with higher specificity than nuclear viability tests but lower sensitivity.[49,55]

Magnetic resonance imaging with gadolinium assesses the extent of infarction. Segments with significant wall thinning (<6 mm) and ≥50% transmural scar have a low likelihood of improvement after revascularization and are considered nonviable.[49,56] A sensitivity and specificity of 84% and 63%, respectively, was reported for this method[49] (Table 2).

Clinical Value of Viability Tests

A large body of observational nonrandomized studies suggested the value of myocardial viability tests for estimating the prognosis of patients with ischemic cardiomyopathy treated with revascularization compared to medical therapy.[47,57,58] Here we will discuss 2 important studies that call into question the benefit of myocardial viability tests and the caveats within.

A landmark trial to study the clinical impact of viability tests was the PET And Recovery following Revascularization 2 (PARR-2) study, which randomized 430 patients with ischemic cardiomyopathy into a positron emission tomography guided-therapy group and a standard care group. Overall, there was no difference in the cardiac outcome at 1 year.[59] However, recommendations from the radionuclide study were not followed in 25.7% of the patients in the imaging-guided arm.[59] A post hoc analysis (Ottawa-FIVE) included the subset of 111 patients enrolled at the University of Ottawa Heart Institute, in which the imaging guidance was followed. This analysis showed a significant reduction of composite cardiac events in the imaging-guided arm (hazard ratio [HR] = 0.37, P = .009).[60] This study remains the only randomized study to date that has used positron emission tomography to guide revascularization strategy.

The Surgical Treatment for Ischemic Heart Failure (STICH) Trial tested the survival benefit of coronary artery bypass grafting for patients with ischemic cardiomyopathy.[61] A total of 601 patients from the 1212 patients enrolled in the trial underwent single photon myocardial perfusion imaging or dobutamine stress echocardiography to test for myocardial viability after randomization. Surgical revascularization plus medical therapy offered a survival benefit over medical therapy alone, but the myocardial viability results had no significant impact on the benefit of revascularization.[62] This study has met criticism for several reasons.[63,64] The STICH viability study was observational and potentially affected by selection bias because viability imaging was nonrandomized and performed in only half of the 1212 enrollees. Further, because 81% of patients had positive viability tests, the study was judged to be underpowered to address the importance of viability testing.[63] Finally, the methods for assessing viability did not include positron emission tomography or magnetic resonance imaging, which are more sensitive methods. Recent but nonrandomized studies using positron emission tomography have lent support to the concept of testing ischemia and viability in ischemic cardiomyopathy.[58,65] Thus, the weight of evidence supports the value of viability testing for defining the likelihood of major adverse cardiac events and functional recovery following revascularization in ischemic cardiomyopathy.

CONCLUSION

Scintigraphic methods play pivotal roles in the clinical diagnosis and management of coronary artery disease.

^{99m}Tc-based myocardial perfusion imaging is widely available and has ample data for judging prognosis, whereas positron emission imaging offers greater accuracy for diagnosing coronary artery disease and myocardial viability. Scintigraphic methods and others, such as stress echocardiography, cardiac computed tomography angiography, and cardiac magnetic resonance imaging, have different profiles of advantages and disadvantages. The choice of a specific diagnostic test should be tailored to the individual patient as well as facility resources. The field of test interpretation has evolved from simply detecting the presence of obstructive coronary artery disease to the evaluation of patient outcomes. Illustrating this are 2 issues: 1) the selection between functional stress testing versus anatomic definition (using coronary computed tomography angiography) for the diagnosis of coronary artery disease and 2) the use of myocardial viability testing in predicting outcomes following revascularization.

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