Myocardial Perfusion Imaging Using Positron Emission Tomography

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ABSTRACT: Coronary artery disease (CAD), also known as ischemic heart disease, is a major cause of morbidity and mortality worldwide, and timely noninvasive diagnosis of clinical and subclinical CAD is imperative to mitigate its burden on individual patients and populations. Positron emission tomography (PET) is a versatile tool that can perform relative myocardial perfusion imaging (MPI) with high accuracy; furthermore, it provides valuable information about the coronary microvasculature using rest and stress myocardial blood flow (MBF) and coronary flow reserve (CFR) measurements. Several radiotracers are approved by the US Food and Drug Administration to help with MPI, MBF, and CFR evaluation. A large body of evidence indicates that evaluation of the coronary microcirculation using MBF and CFR provides strong diagnostic and prognostic data in a multitude of patient populations. This review describes the technical aspects of PET compared to other modalities and discusses its clinical uses for diagnosis and prognosis of coronary arterial epicardial and microcirculatory disease.

INTRODUCTION

Coronary artery disease (CAD) is one of the major causes of morbidity and mortality in both developed and developing countries. Despite the fact that mortality rates have dropped over the past several decades, CAD remains solely responsible for at least a third of all deaths in middle-aged and older individuals.[1] Furthermore, it is expected that one-third to one-half of middle-aged adults living in the United States will develop a manifestation of CAD at some point in their lifetime.[2] Therefore, timely diagnosis of both clinical and subclinical CAD through noninvasive means plays an important role in mitigating its large burden on a multitude of patients and patient populations.

DIAGNOSTIC TOOLS FOR ASSESSING CAD

Several tools are currently available for assessing suspected CAD. The most common and widely available one globally is exercise electrocardiography, which evaluates exercise capacity in addition to symptoms. However, it is limited by its low sensitivity and specificity.[3] Exercise and dobutamine stress echocardiography are widely used CAD assessment tools with a well-established impact on patient prognosis and outcomes.[4] In addition to its decent diagnostic accuracy, a normal stress echocardiogram was shown to confer a very low risk of future cardiac events. It is important to mention, however, that local laboratory expertise and image quality have been known to negatively impact the diagnostic accuracy of stress echocardiography.

Coronary computed tomography angiography (CTA) is an anatomic noninvasive tool that has high sensitivity and acceptable specificity for detecting obstructive CAD. However, the diagnostic accuracy of CTA is reduced in the presence of significant coronary calcification and elevated heart rate and usually leads to overestimation of stenosis severity.[5]

Single photon emission computed tomography (SPECT) for myocardial perfusion imaging (MPI) is the most commonly used tool in the United States for assessing suspected CAD. It is widely available and offers decent diagnostic accuracy with reported sensitivity of 80% to 85%.[6] However, positron emission tomography (PET), a fairly recent myocardial nuclear perfusion imaging modality, has several advantages over SPECT (Table 1). The photon energy of PET radiotracers is 511 KeV versus 80 to 140 KeV for SPECT, leading to lower radiotracer injection requirements (ie, less patient radiation) and less tissue attenuation.[7] In addition, since the most commonly used PET radiotracers have a significantly shorter half-life compared to their SPECT counterparts, PET studies can be performed in a shorter time and with lower overall radiation exposure. The shorter tracer half-life, however, will generally favor pharmacological over exercise stress testing when PET imaging is employed. Finally, image spatial resolution is significantly higher in PET compared to SPECT, although this is secondary to tracer properties and scanner-related factors.

POSITRON EMISSION TOMOGRAPHY

The interest in PET MPI has increased throughout the past few decades. Performed mostly in conjunction with PET-CT systems, PET MPI can assess relative perfusion, absolute myocardial blood flow at stress and rest, coronary flow reserve,

CHARACTERISTIC	SPECT	PET
Radiotracer	Generator	Generator/cyclotron
Energy	80-140 KeV	511 KeV
Attenuation	More	Less
Half-life	6-72 hours	1.5-13 minutes
Radiation	Greater	Significantly less
Study duration	3-4 hours	30-40 minutes
Stress	Exercise > pharmacological	Pharmacological only in clinical use

Table 1.
SPECT versus PET radiotracers and technical characteristics. SPECT: single photon emission computed tomography; PET: positron emission tomography; KeV: kiloelectron volts

left ventricular ejection fraction, possible ischemic dilatation, and coronary artery calcium levels.[7] The resulting images are all acquired within 20 minutes and provide valuable corroborating information to accurately assess and manage patients with suspected or known CAD.

PET Radiotracers

Positron emission tomography offers a relatively high spatial and temporal resolution that, combined with low radiation delivery, makes it an attractive modality for assessing suspected or known CAD through noninvasive myocardial blood flow (MBF) and coronary flow reserve (CFR) measurements. Two radiotracers are currently used in clinical practice: Nitrogen-13 ammonia (^{13}N-ammonia) and ^{82}rubidium.[7] Oxygen-15 water (^{15}O-water) is used outside of the United States to assess MBF but is not approved by the US Food and drug administration for clinical use in the United States. Both ^{15}O-water and ^{13}N-ammonia MBF patterns have been validated against radioactive microspheres in animal models.[8] On the other hand, ^{82}rubidium has been mainly validated against ^{13}N-ammonia.

^{15}O-water is an inert and freely diffusible molecule that has a linear relation to MBF with an almost-perfect first-pass tissue extraction, making it the gold standard for MBF evaluation.[9,10] However, its low signal-to-noise ratio profile, need for an onsite cyclotron, and short half-life (2.09 min) limit its use in daily clinical practice. In comparison, ^{13}N-ammonia and ^{82}rubidium, which are the two most widely used tracers in daily clinical practice, have a nonlinear MBF profile. The first-pass retention fraction for ^{13}N-ammonia and ^{82}rubidium at rest is 85% and 65%, respectively, with a declining retention rate at higher blood flow.[11] The excellent image quality of ^{13}N-ammonia allows for the adequate evaluation of ischemia (due to its positron range), while its relatively long half-life (~10 min) permits exercise and vasodilator stress testing. However, the need for an onsite or nearby cyclotron for the production of ^{13}N-ammonia is a hurdle for its widespread use. ^{82}Rubidium is a potassium analogue requiring active transport inside the cell via a functional Na-K ATPase pump. Being produced by a generator (as opposed to a cyclotron) makes it more appealing for widespread clinical use (Figure 1). The ^{82}rubidium tracer performs similarly to ^{13}N-ammonia in terms of its diagnostic accuracy; however, its short half-life of 76 seconds allows for quick repeat imaging during stress in almost matching physiologic states.[11,12] Figure 2 depicts a regadenoson-based PET MPI protocol, but other stress pharmacological agents such as adenosine and dipyridamole could also be used. Finally, given its longer positron range, ^{82}rubidium has a lower spatial resolution compared to ammonia. A summary of the available radiotracer characteristics is listed in Table 2.[13]

Flurpiridaz, an 18F-based tracer with a 110-minute half-life, is currently being studied in a phase 3 trial. It is usually supplied in unit doses and may be combined with exercise stress testing with PET.[14]

Diagnostic Accuracy of PET Myocardial Perfusion Imaging

Several studies have evaluated the diagnostic accuracy of PET MPI for diagnosing obstructive CAD.[7] Overall, PET MPI has an average

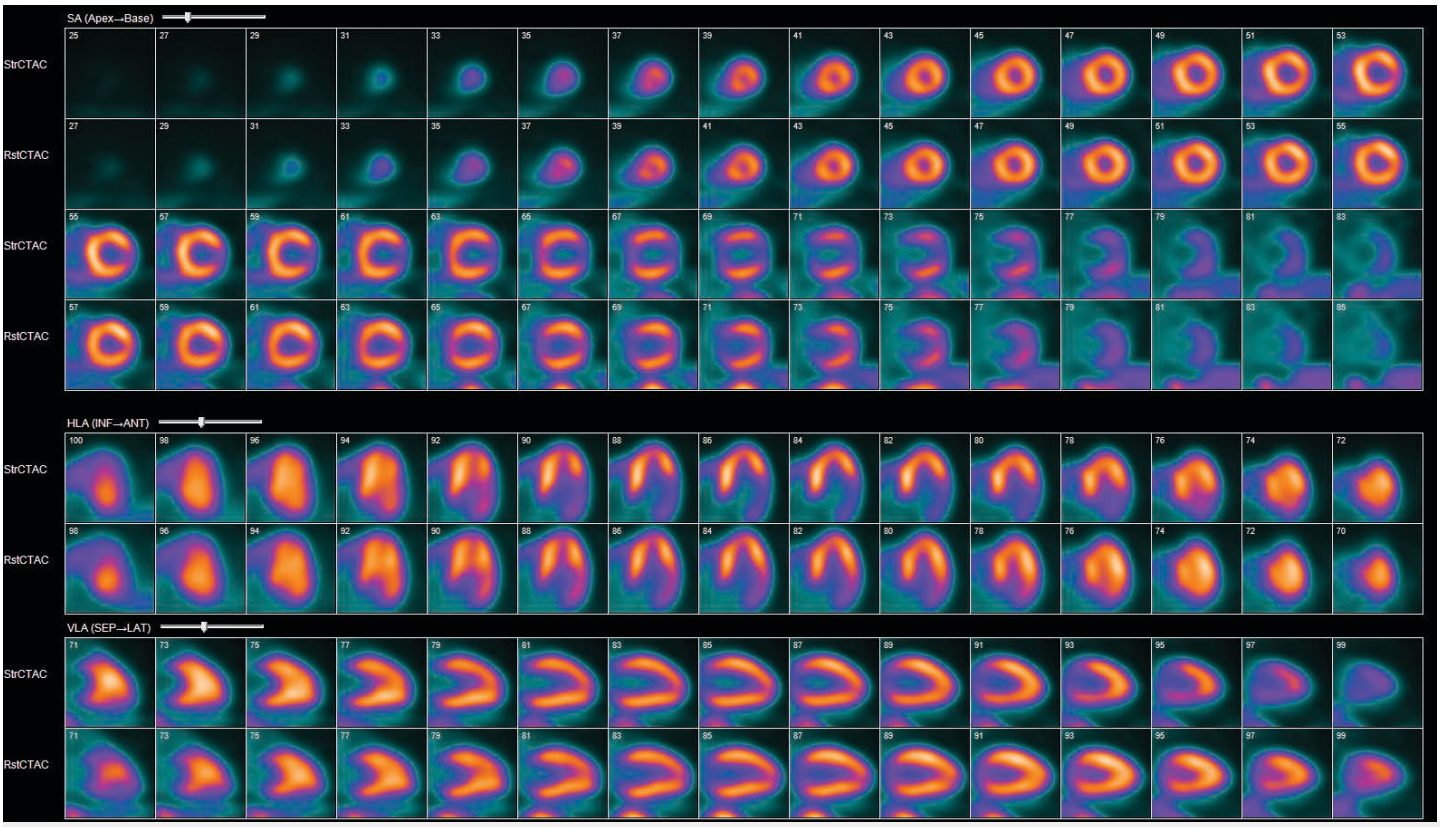

Figure 1.
Positron emission tomography ^{82}rubidium scan depicting moderate myocardial ischemia in the lateral wall. Rows 1,3,5,7 were obtained at peak stress, whereas rows 2,4,6,8 show the corresponding rest images. SA: short axis; HLA: horizontal long axis; VLA: vertical long axis

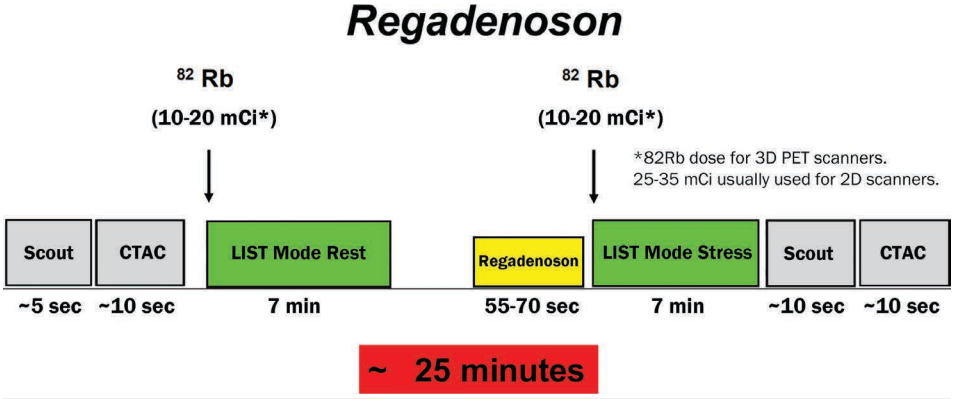

Figure 2.
Currently employed PET MPI pharmacological (regadenoson) stress protocol. The use of 3-dimensional scanners equipped with digital detectors has allowed for the lowering of delivered ^{82}rubidium dose down to between 10 and 20 mCi. PET: positron emission tomography; MPI: myocardial perfusion imaging; 82 Rb: ^{82}rubidium; CTAC: computed tomography attenuation correction; CAC: coronary artery calcium

90% sensitivity for detecting at least one coronary artery with > 50% stenosis, with an average specificity of 89%. This yields a positive and negative predictive value of 94% and 73%, respectively, with a diagnostic accuracy of 90%. Importantly, PET MPI sensitivity of obstructive CAD detection remains high in single versus multivessel disease, in obese individuals, and in both men and women.[15] It is worth noting, however, that most of the available accuracy data pertains to PET scanners equipped with radionuclide attenuation correction and using pharmacologic (vasodilator) stress rather than exercise.

Prognostic Value of PET Myocardial Perfusion Imaging

Multiple studies have confirmed the prognostic value of PET MPI. In a large

CHARACTERISTIC	^{82}RUBIDIUM	^{13}N-AMMONIA	^{15}O-WATER
Supplied	Generator	Cyclotron	Cyclotron
Half-life	76 s	9:96 min	2.09 min
Uptake mechanism	Active extraction	Active extraction	Freely diffusible
Positron range in water	1.6 mm	0.28 mm	0.5 mm
Image quality	Very good	Excellent	Uninterpretable
Radiotracer uptake characteristics	Adequate	Very good	Excellent

Table 2.
Characteristics of available positron emission tomography radiotracers. Reproduced with permission from Al Badarin et al.[13]

multicenter study of more than 7,000 patients, there was an increased event rate in patients with perfusion defects compared to patients without perfusion defects. The hazard of cardiac events increased as the size of perfusion defects increased.[16] Similarly, a drop in left ventricular ejection fraction detected by PET was associated with worse outcomes. A recent large study with more than 16,000 patients confirmed these findings and showed that patients with 5% or more ischemia had improved survival with early revascularization.[17]

PET-Derived Myocardial Blood Flow

In addition to its enhanced spatial resolution and improved workflow, PET MPI allows for assessment of MBF and CFR. Myocardial blood flow measurements are derived using dynamic PET images of the myocardium after the application of well-validated mathematical models.[13] Dynamic PET imaging is a rapid image acquisition mode that starts around 10 seconds before radiotracer injection, allowing for real-time tracking of the tracer as it flows between the blood and myocardium. Because these acquisitions are performed at rest and then during maximum hyperemia, both rest and stress MBF can be quantified to enable calculation of the CFR (as the ratio of the stress/rest MBF). Both ^{13}N-ammonia and ^{82}rubidium tracers have been well-studied and validated for MBF calculation.[18]

At least five quantification models for MBF calculation are available for ^{82}rubidium, but the 1-tissue compartment model is the simplest and most used (Figure 3). Although most of these models deliver different estimation results of rest and peak MBF, the differences in CFR remain relatively minimal. Furthermore, Murthy et al. demonstrated in a large cohort of patients that the prognostic ability of CFR remains unchanged irrespective of the model employed.[19]

The current American Society of Nuclear Cardiology guidelines suggest that MBF measurement is useful in the following clinical scenarios[18]:

- Patients without known prior CAD presenting with symptoms suspicious of myocardial ischemia.
- Patients with known CAD whereby a more detailed physiological assessment is anticipated.
- Patients with an elevated suspicion for significant left main or multivessel CAD.
- Patients with a discrepancy between an abnormal relative perfusion scan in the setting of nonobstructive coronaries on invasive coronary angiogram in order to assess possible microvascular dysfunction.
- Patients with prior heart transplantation where cardiac allograft vasculopathy needs to be ruled out.

The guidelines also list the following clinical scenarios in which caution is highly advised when interpreting MBF results:

- Post-coronary artery bypass graft surgery where MBF reduction can be seen despite patent grafts.
- Patients with known large infarcts where resting MBF may be severely reduced so that a small increase in flow during stress imaging could lead to normal or near-normal flow reserve.
- Patients with advanced chronic kidney disease who usually have diffuse coronary disease.
- Patients with known dilated cardiomyopathies and/or severe left ventricular dysfunction.

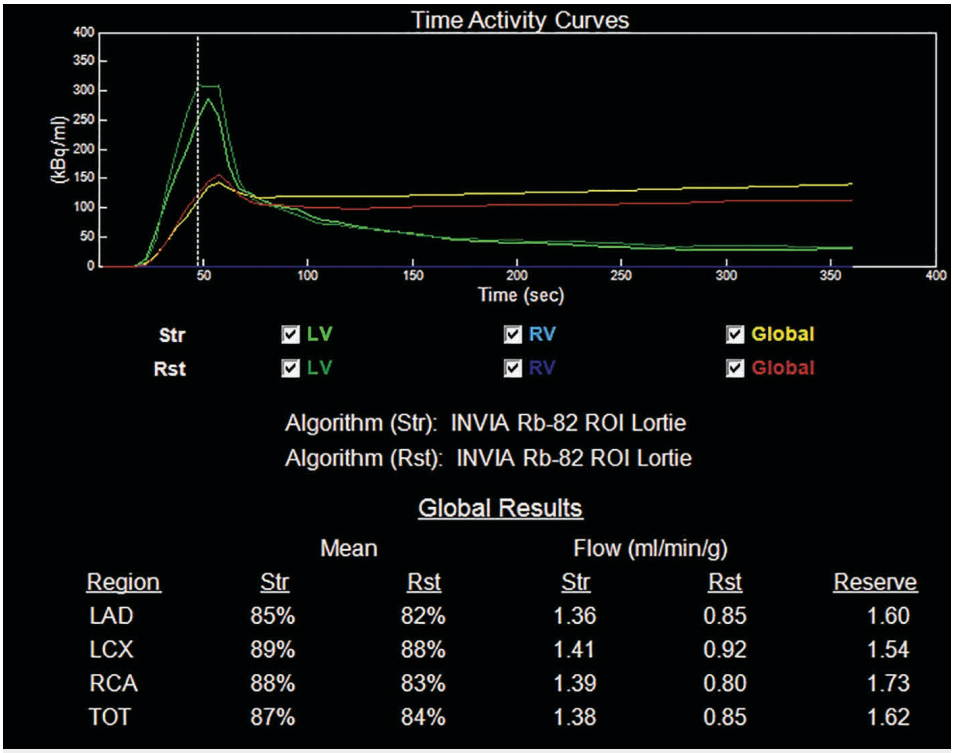

Figure 3.
Time-activity curves for the assessment of myocardial blood flow in a patient with nonobstructive coronary artery disease on coronary angiogram. The global coronary flow reserve is reduced, indicating microvascular dysfunction. Several models are available for coronary flow reserve estimation, but the 1-tissue compartment model depicted in this figure is the most widely employed. Str: stress; Rst: rest; LV: left ventricle; RV: right ventricle; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TOT: total

Correlation between CFR and FFR

The hemodynamic severity of a coronary lesion can be assessed using both fractional flow reserve (FFR) and CFR.[20] The use of FFR has a Class I indication from various guideline committees, making it a widely adopted technique for stenosis assessment. These guideline recommendations were mainly based on the FAME (Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation) study, a randomized multicenter trial that evaluated the safety and outcomes of deferring angioplasty for lesions not deemed hemodynamically significant using an FFR cut-off of 0.80.[20] As opposed to CFR, which estimates the ratio of total coronary blood flow with maximal hyperemia compared to rest flow, FFR is a lesion-specific measure of the pressure drop across a stenotic lesion that is limiting blood flow. Therefore, CFR is a measure that reflects the burden of CAD throughout the entire coronary tree, whereas FFR is a measure of lesion-specific ischemia. FFR is mainly used to determine the need for revascularization of one or more defined lesions, while CFR estimates the patient's global risk since it reflects the combined effect of disease in the macro and microcirculation. Not surprisingly, inconsistencies between FFR and CFR have been reported, mainly owing to the physiological entities that these parameters reflect–namely, focal lesions for FFR and diffuse epicardial or microcirculatory disease for CFR. Patients with single-vessel disease, however, have shown good correlation between CFR and FFR,[21] while the correlation in those with multivessel disease is much weaker. More importantly, combining CFR and FFR measures provides a valuable opportunity to better understand coronary physiology and to identify and tailor novel targets for medical intervention.[22]

PET VERSUS SINGLE PHOTON EMISSION TOMOGRAPHY IN SPECIFIC CLINICAL SCENARIOS

Diagnosis of Left Main and Multivessel CAD

A wealth of evidence has accumulated over the years supporting the role of SPECT MPI for CAD risk stratification and revascularization guidance. However, underestimation of the true severity of CAD remains the Achilles' heel of relative MPI. For example, hemodynamically significant left main or three-vessel stenosis can lead to a state of balanced flow reduction, whereby a perfusion defect may go undetected in the setting of a relative perfusion imaging modality. Only 56% of patients with known significant left main stenosis showed high-risk SPECT scans. However, when combining nonperfusion variables (such as transient ischemic dilation), 83% of patients were identified as high risk.[23] Therefore, the diagnostic yield for left main stenosis can be ameliorated by using additional nonperfusion parameters. Since PET MPI provides accurate information about left ventricular ejection fraction reserve at rest and at real peak stress, it offers incremental diagnostic information for detecting significant left main disease. This feature, which is not achievable on SPECT, gives PET superior diagnostic accuracy when it comes to three-vessel and left main disease detection.[24,25]

Furthermore, PET's role in diagnosing significant obstructive CAD is further solidified by its advantage over SPECT when it comes to measuring MBF and CFR parameters. These play an important complimentary role in identifying high-risk coronary anatomy when relative MPI shows normal or minimally abnormal perfusion patterns. In a study of 120 patients who underwent ^{82}rubidium PET MPI, most patients with multivessel CAD had reduced CFR (< 2). Importantly, while preserved CFR confers a low likelihood of multivessel CAD or left main disease (97% negative predictive value),[26] a reduced CFR could be nonspecific; therefore, depending on the clinical scenario, other causes such as diffuse endothelial dysfunction need to be considered.

Detection of Subclinical CAD and Microvascular Dysfunction

The ability to diagnose subclinical CAD is a robust feature of PET imaging. Relying solely on stress-induced relative perfusion imaging, as is the case in SPECT, allows for the diagnosis of epicardial coronary flow-limiting stenosis but misses possible underlying early nonobstructive disease. In fact, studies have demonstrated the high prevalence of subclinical CAD (coronary calcifications or endothelial dysfunction) in patients with normal myocardial perfusion.[27] The ability of PET to provide MBF and CFR measurements gives it an advantage over SPECT to assess cardiovascular health beyond the epicardial coronary tree. Multiple studies have shown that an attenuated MBF response, and hence a low CFR, is more prevalent among patients with multiple cardiovascular risk factors in the absence of overt CAD or even angiographically significant epicardial coronary stenoses, and that a reduced CFR confers an increased risk of adverse cardiovascular events.[7] Thus, the ability of PET imaging to uncover early subclinical CAD using noninvasive means not only identifies higher-risk patients—who may be eligible for more aggressive risk-factor control and early implementation of therapeutic strategies—but also enables serial follow-up on these interventions, as shown in some studies that demonstrated favorable changes in CFR following adequate interventions.[28]

The Incremental Value of Coronary Artery Calcium Score

The coronary artery calcium score can often be performed with PET MPI since most PET scans have a CT system performed for attenuation correction. This system can be used for a gated chest CT to detect coronary artery calcium. Prior data have already demonstrated the diagnostic and prognostic value of a coronary artery calcium score over MPI. While this is more extensively studied in the SPECT literature, there are few studies in the PET literature to suggest that patients with normal perfusion and an elevated coronary artery calcium score do significantly worse compared to those with normal perfusion and a low calcium score.[27]

Risk Stratification Using PET-Derived MBF and CFR

The ability of PET to detect subclinical CAD using MBF and CFR makes it a strong prognostic tool for predicting future major adverse cardiac events (MACE). Studies have shown that PET-derived MBF and CFR measurements offer incremental risk stratification beyond known traditional risk factors.[29] For example, a CFR value < 1.6 on both ^{13}N-ammonia and ^{82}rubidium PET demonstrated an independent ability to predict future MACE.[30,31] In addition, in one study PET-derived CFR identified patients who would benefit from early revascularization and subsequent improvement in symptoms and survival.[30]

Importantly, these prognosis results seem to extend to a multitude of patient populations, with the risk stratification power of MBF and CFR further established in patients who are women or have chronic kidney disease or diabetics.[32,33] Interestingly, one study found CFR to be strongly associated with elevated cardiac troponin in patients who had stable chest pain in the setting of non–flow-limiting CAD. Furthermore, the CFR value was able to modify the impact of troponin elevation on MACE, as patients with preserved CFR (≥ 2) had significantly lower event rates compared to those with reduced CFR.[28]

CONCLUSION

The choices of noninvasive perfusion and functional parameters provided by PET imaging—including relative perfusion patterns, MBF and CFR, calcium scoring, and left ventricular ejection fraction reserve—gives it a significant advantage over SPECT in diagnosing and detecting the wide spectrum of CAD, from early subclinical endothelial dysfunction to severe multivessel or left main disease.

KEY POINTS

- Cardiac positron emission tomography (PET) is currently the most accurate noninvasive test for the evaluation of coronary artery disease.
- Adding calcium scoring to myocardial perfusion PET will enhance its diagnostic and prognostic value.
- PET myocardial blood flow measurement is a unique feature of this modality and is most useful in assessing possible microvascular dysfunction and in patients without known prior coronary disease presenting with symptoms suspicious of myocardial ischemia, those with elevated suspicion for significant left main or multivessel coronary disease, and those with prior heart transplantation where cardiac allograft vasculopathy must be ruled out.

Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:
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