Fluorodeoxyglucose Applications in Cardiac PET: Viability, Inflammation, Infection, and Beyond

Shaden Khalaf, MD; *Mouaz H. Al-Mallah,* MD, MSc

HOUSTON METHODIST DEBAKEY HEART & VASCULAR CENTER, HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS

ABSTRACT: With its high temporal and spatial resolution and relatively low radiation exposure, positron emission tomography (PET) is increasingly being used in the management of cardiac patients, particularly those with inflammatory cardiomyopathies such as sarcoidosis. This review discusses the role of PET imaging in assessing myocardial viability, inflammatory cardiomyopathies, and endocarditis; describes the different protocols needed to acquire images for specific imaging tests; and examines imaging interpretation for each image dataset—including identification of the mismatch defect in viability imaging, which is associated with significant improvement in LV function after revascularization. We also review the role of fluorodeoxyglucose PET in cardiac sarcoidosis diagnosis, the complementary role of magnetic resonance imaging in inflammatory cardiomyopathy, and the emerging use of cardiac PET in prosthetic valve endocarditis.

INTRODUCTION

The use of positron emission tomography (PET) has been increasing with regard to cardiac patients, especially those with myocarditis, endocarditis, and sarcoidosis. PET has coronary applications, such as detecting coronary artery disease using flow tracers, and can also help determine viability, inflammation, and infection using metabolism tracers.[1] This paper highlights the importance of PET imaging in the assessment of myocardial viability, inflammatory cardiomyopathies such as sarcoidosis, and valvular- and device-related infections.

CARDIAC PET IN VIABILITY IMAGING

It is well recognized that myocardial tissue has unique metabolic properties that allow it to adapt to acute and chronic changes in coronary blood flow. Viable myocardial tissue includes cells with preserved cell membrane integrity regardless of the presence of concomitant reversible metabolic changes.[2] For example, in chronic myocardial ischemia, the sustained decline of myocardial blood flow leaves some cells in a reversible hibernating state with preserved structural integrity despite the reduced blood flow.[3] These cells adapt by decreasing their energy consumption and have a high likelihood of functional recovery if revascularization occurs within an appropriate timeframe. It should be noted that myocardial tissue consumes long-chain fatty acids as its preferred source of metabolic substrate. Under anaerobic condition (ie, an ischemic state with decreased myocardial perfusion), the myocardial cells resort to glucose as their primary energy source. Active glucose uptake into myocardial tissue is also mediated by insulin secretion. These biochemical phenomena serve as the backbone of PET viability imaging.[4]

PET relies on the metabolic and perfusion properties of myocardial tissue to delineate viable from nonviable/scarred tissue and to guide medical and surgical decision making in patients with ischemic heart disease. It requires coupling of resting myocardial perfusion studies, which are commonly performed using rubidium-82 and nitrogen-13 ammonia, with metabolic imaging that is usually glucose based.[2] 18F-fluorodeoxyglucose (FDG) is the primary radiolabeled glucose analog used to assess viability. Alternate radiotracers such as carbon-11 acetate are mainly used in the research arena. Myocardial segments that have normal resting flow and/or uptake FDG are deemed to have preserved glucose metabolism and are generally viable. The presence of a mismatch defect due to decreased myocardial blood flow but intact metabolism is critical for determining contractility recovery post revascularization. Those segments without FDG uptake and reduced myocardial blood are called matched defects and are likely nonviable.[5]

PROTOCOLS FOR VIABILITY IMAGING

Patient preparation is key to the success of PET viability imaging, and it involves multiple protocols, all of which require a 6- to 12-hour fast.[6] The most common protocol uses an oral glucose load to induce an endogenous insulin response. The dose of glucose loading varies between 25 and 100 g depending on the patient's baseline fasting glucose level. The glucose load effectively elevates transient plasma glucose, thereby stimulating pancreatic insulin production; this, in turn, reduces fatty acid utilization by the myocardium and enhances myocardial glucose utilization. This necessitates achieving a euglycemic state prior to the FDG injection. More often than not, intravenous insulin is required following the oral insulin

load. The glucose clamp technique is used by many providers and is preferred for individuals who are unable to swallow or have difficulty completing an oral preparation. It is also the protocol of choice in advanced diabetic patients. Because the glucose clamp is a labor-intensive protocol, most labs default to an oral glucose load for logistical purposes. Several centers in Europe, however, use Acipimox, which is a nicotinic acid derivative. While it has not been approved by the US Food and Drug Administration, Acipimox is reported to impede peripheral lipolysis, lower plasma free fatty acid levels, and stimulate utilization of myocardial glucose.

Diabetics pose a challenge for FDG imaging because of alterations in insulin production and insulin resistance. This situation is magnified in diabetic patients with high basal insulin requirements. However, a number of imaging protocols are designed to help diabetic patients, the most widely used being the hyperinsulinemic-euglycemic clamp. This approach requires close monitoring of the patient's glucose levels because it stimulates the uptake of glucose by titrating exogenous insulin. The target plasma glucose level must be between 100 and 140 mg/dL before injecting the FDG. Most often, these approaches result in diagnostic images. The FDG dose ranges between 5 and 15 mCi depending on the sensitivity of the PET system used. Patients are monitored 45 to 90 min after FDG administration; during this time, myocardial FDG uptake increases while blood pool content decreases. Patients are then imaged for a typical duration of 10 to 30 minutes.

Perfusion images and metabolism scans are aligned and interpreted simultaneously to reveal four possible patterns of myocardial perfusion/metabolism:

1. Normal myocardium, with normal perfusion and FDG uptake.
2. Mismatch pattern, which shows abnormal/reduced perfusion with normal FDG uptake; this pattern denotes hibernating myocardium and is highly likely to recover after revascularization (Figure 1).
3. Matched pattern, in which an absent/reduced perfusion scan with absent/proportionally reduced FDG uptake is consistent with scared myocardium; this pattern has a low likelihood of recovery following revascularization (Figure 2).
4. Reversed mismatch pattern. In this pattern, normal myocardial perfusion with reduced FDG uptake (usually in the septal wall) occurs in the context of a left bundle branch block. This pattern has also been described in the setting of myocardial stunning or significant insulin resistance.

The results of the viability study are often used to guide management and help predict short- and long-term outcomes.

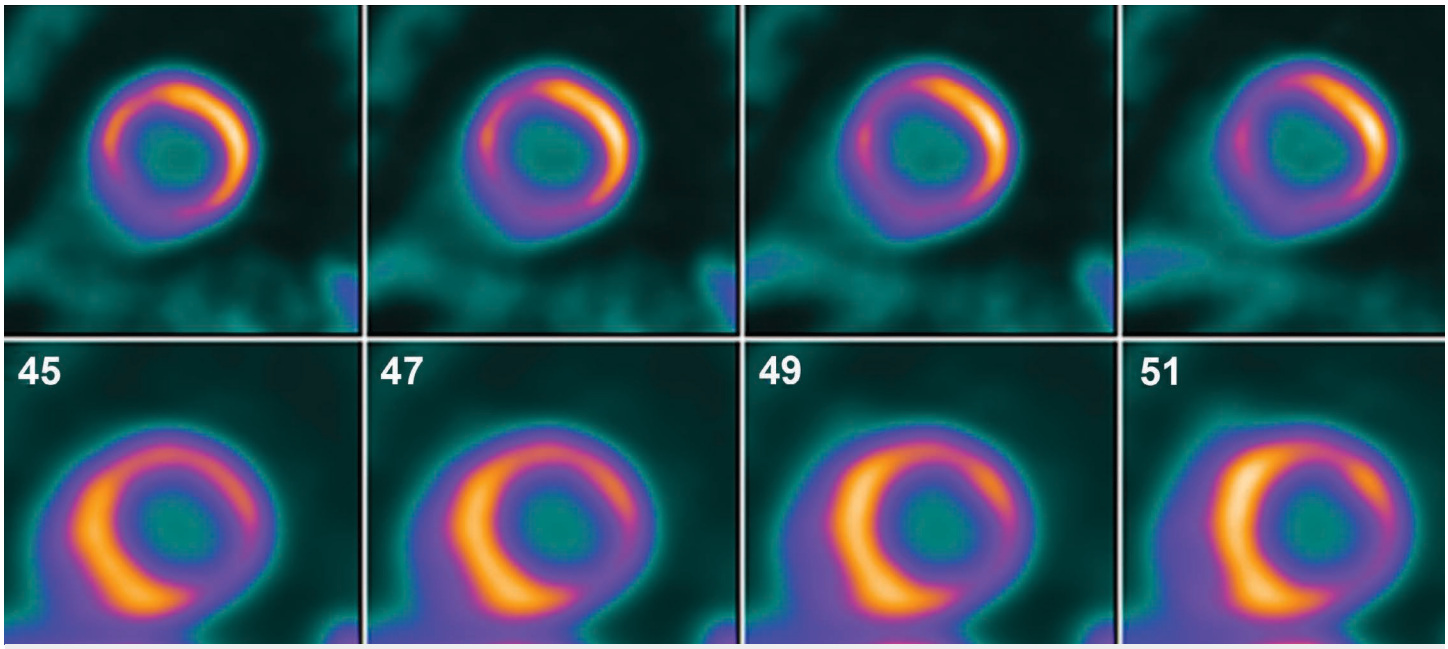

Figure 1.
An example of a perfusion-metabolism mismatch. The lower row shows the perfusion images with a large anterolateral and inferolateral perfusion defect that has normal metabolic activity (as seen on metabolic images using fluorodeoxyglucose positron emission tomography imaging on the upper row). The anterolateral and inferolateral walls are viable.

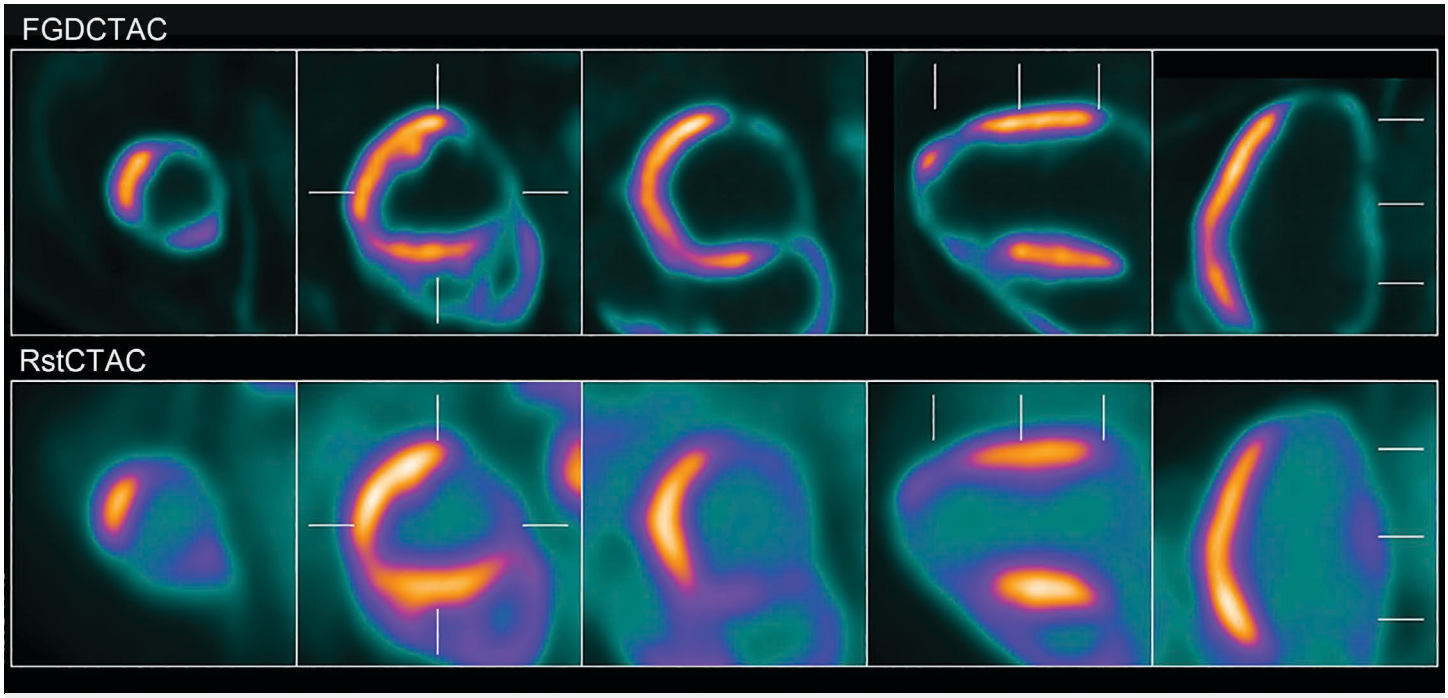

Figure 2.
Matched defect between perfusion and metabolic images. There is a severe perfusion defect in the entire inferior wall and apical walls, with no fluorodeoxyglucose (FDG) uptake in the same area of perfusion defect, suggesting near-transmural scarring in this territory. CTAC: computed tomography attenuation correction.

For example, patients with viable myocardium who are managed medically have higher short-term cardiovascular mortality.[4] Multiple single-center studies have been published about the role of myocardial viability in managing patients with ischemic cardiomyopathy,[7] and while most of these have been small, observational, and nonrandomized, in aggregate they suggest a survival benefit with revascularization in patients who have hibernating/ischemic myocardium. The PET and Recovery Following Revascularization-2 (PARR-2) trial is the only large randomized multicenter trial designed to evaluate the efficacy of a combined FDG–PET-guided strategy for patients with severe cardiomyopathy and suspected CAD.[8] Over a 4-year period, the study enrolled and randomized 430 participants to FDG–PET-assisted management or standard of care. Those receiving FDG–PET-assisted management showed a nonsignificant trend toward a reduction in the primary composite end point (cardiac death, myocardial infarction, or cardiac re-hospitalization for angina or heart failure) at 12 months follow-up (HR 0.78; 95% CI, 0.58-1.1, $P = .15$). However, in a post hoc analysis, patients who adhered to PET recommendations for revascularization showed a significant reduction in adverse events (HR 0.62; 95% CI, 0.42-0.93, $P = .019$), with benefits extending to 5 years. One of the key limitations of this study was significant nonadherence to therapeutic strategies recommended by PET, which was seen in 25% of participants. Furthermore, the varying degree of resources and experience among the participating centers may have had an impact on decision making.

Given the above, the American College of Cardiology (ACC) and American Heart Association (AHA) published a guideline on the management of heart failure stating that the use of noninvasive imaging is reasonable for detecting myocardial ischemia and viability in patients with de novo heart failure, and with known CAD and no angina, unless the patient is not a candidate for revascularization (Class IIa, Level of Evidence C).[9,10] The appropriate-use criteria endorsed by many professional societies suggests that in most clinical scenarios, it is appropriate or potentially appropriate to assess myocardial viability in advance cardiomyopathy, and the ACC/AHA guidelines leave the choice of modality to the treating physician's discretion. It is worthwhile to note that technological advances and the advent of hybrid PET/magnetic resonance systems have greatly expanded the options for advanced imaging, allowing for anatomical, functional, tissue characterization, and metabolic perfusion data in one setting. The benefits of these systems will most likely be seen in the assessment of myocardial viability and inflammatory cardiomyopathy.[11,12]

SARCOIDOSIS AND INFLAMMATORY CARDIOMYOPATHIES

Cardiac PET is also being used to assess inflammatory cardiomyopathies. Sarcoidosis, a systemic inflammatory disorder with variable clinical presentations, is regarded as a representative of these inflammatory cardiomyopathies. Cardiac sarcoidosis (CS) is commonly associated with conduction disturbances and ventricular arrhythmias. The clinical and imaging criteria for diagnosis set by the Heart Rhythm Society consensus paper include the following[13]:

1. Identification of noncaseating granulomas on histopathology in different tissues.
2. Corticosteroid or immunosuppressive therapy responsive cardiomyopathy or heart block.
3. Unexplained reduced left ventricular systolic function (LVEF < 40%).
4. Unexplained sustained ventricular tachycardia (VT), advanced atrioventricular block (Mobitz type II second-degree heart or third-degree block).
5. Patchy uptake of cardiac FDG-PET in a pattern consistent with CS.
6. Late gadolinium enhancement on cardiac magnetic resonance imaging in a pattern consistent with CS.
7. Positive gallium uptake in a pattern consistent with CS.

Although the key criterion for this diagnosis is identification of noncaseating granulomas on histopathology, this is not always possible in CS due to its patchy involvement in the myocardium.[14] The diagnostic yield of endomyocardial biopsies is inconsistent with variable sensitivity for the detection of CS. Therefore, the consensus statement emphasized that this criterion applies only if other cardiac causes have been reasonably excluded. Even so, the diagnosis remains challenging and is often missed, only to be identified at the time of autopsy.[15]

Chang et al. described a single-center experience with patients who underwent heart transplantation between 1987 and 2011. Of the 411 patients receiving a transplant, 19 were found to have CS, of which only 4 were diagnosed before the surgery.[16]

As expected, CS has several key patterns on difference imaging modalities. On cardiac magnetic resonance (CMR), late gadolinium enhancement shows patchy hyperenhancement and scarring in a noncoronary artery pattern,[17] although the degree of hyperenhancement may improve on repeat imaging after a trial of steroid therapy.[18] The scarring is commonly

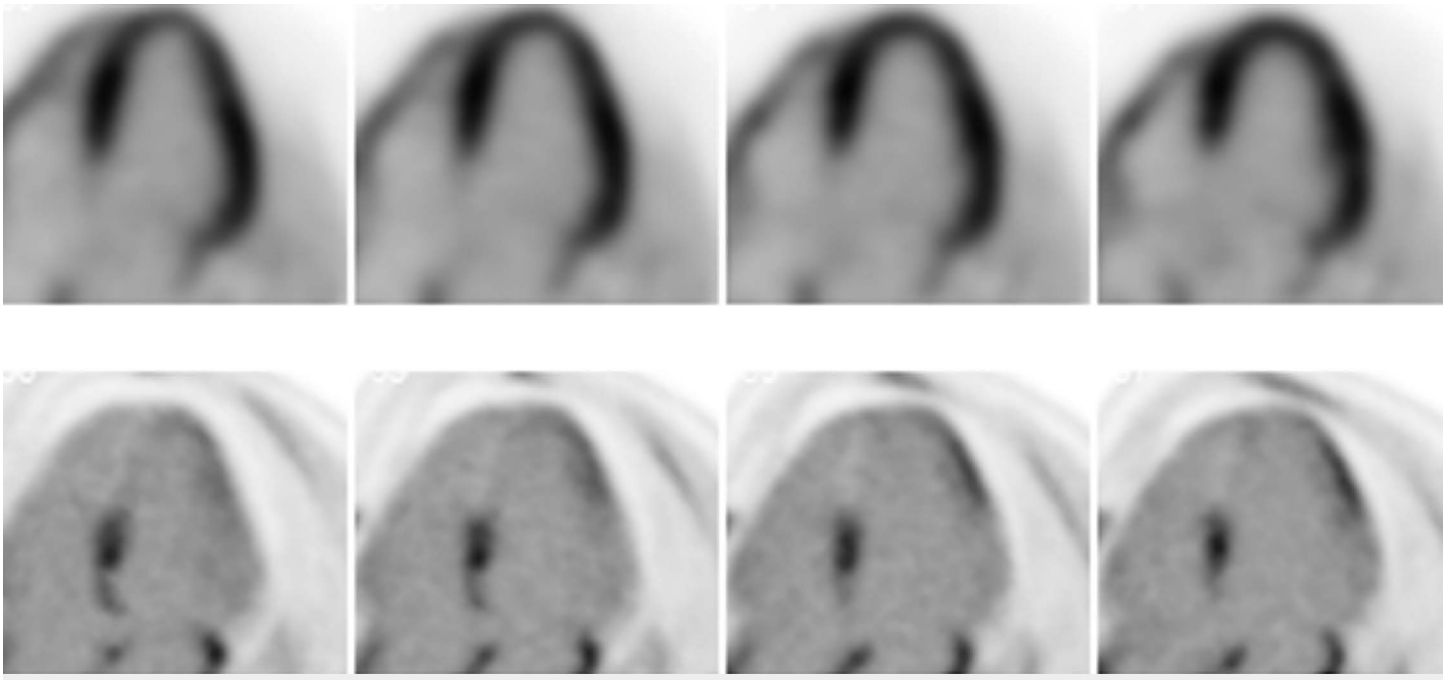

Figure 3.
Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in a patient with suspected cardiac sarcoidosis. Upper rows are FDG images; lower rows are perfusion images. Notice the perfusion defects in the basal septum, proximal anterior wall and apical segments. There is significant FDG uptake in the areas of the perfusion defects, indicating active inflammation.

mid- or epicardial in nature; however, some patients have subendocardial enhancement similar to those with CAD. Delayed enhancement on CMR portends a poor prognosis with decreased event-free survival. However, it does not indicate active inflammatory myocarditis from sarcoidosis or other connective tissue diseases; rather, it indicates that these patients have evidence of prior inflammation in the heart.

Cardiac PET is the primary tool to assess active inflammation. It serves as a powerful and complementary modality, especially in cases where the diagnosis remains uncertain despite initial investigations that include CMR. PET adds incremental value because it detects an active inflammatory process, which increases the likelihood of CS.[19,20] PET also enables one to assess the degree of CS involvement and guides the course of therapy (Figure 3). Additionally, it identifies extracardiac disease that can be potential targets for biopsy (Figure 4).

Dietary preparation is imperative to suppress glucose uptake in normal myocardial cells. Several approaches have been described, with expert consensus favoring a prolonged fast with a high-fat, low-carbohydrate diet. Our institutional protocol instructs patients to follow a high-fat (> 35 grams) and low- (< 3 grams) or preferably no-carbohydrate diet the day prior to the study followed by at least a 12-hour fast. Patients are counseled over the phone 2 days prior to the exam to ensure understanding. The patient's dietary log is reviewed the day of the study to ensure adherence to the regimen.

With advances in technology, CMR and FDG-PET can be used concomitantly to evaluate patients with suspected CS. In a study by Vita et al., 60 out of 91 patients (66%) who showed positive late gadolinium enhancement on CMR had abnormal FDG uptake. Combining the data from CMR and FDG-PET correctly reclassified 12 patients as having a higher likelihood (> 90%) and 16 patients as having a lower likelihood of CS.[21] The overall data suggest that this strategy can enhance the diagnostic accuracy in roughly 80% of cases, which would have significant clinical and therapeutic implications, especially in patients with highly probable CS. Moreover, this can be done simultaneously using PET/MRI systems.[22]

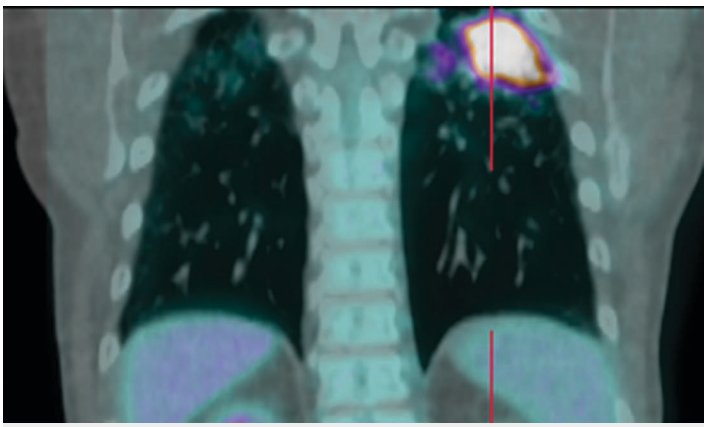

Figure 4.
Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in a patient with known pulmonary sarcoidosis. There is severe intense uptake in the left upper lobe of the lung. This patient had no FDG uptake in the myocardium.

VASCULAR INFLAMMATORY DISEASES

Cardiac PET also assesses cardiovascular inflammation outside the heart, although it should be noted that computed tomography angiography is the primary modality for assessing aortic syndromes due its widespread availability, timeliness in emergent situations, and excellent spatial resolution.[23] Inflammatory conditions of the aorta and intramural hematomas have similar presentations and can mimic aortic dissections. In these clinical situations, FDG-PET can be used to help assess aortic inflammation since FDG accumulates in areas of inflammation (as macrophages) and inflammatory T-cells are glucose avid. These functional properties make this modality very attractive for assessing both aortitis and periaortic inflammations.

FDG-PET can also evaluate for giant cell arteritis and Takayasu arteritis with acceptable specificity and is a promising tool for assessing disease activity and response to therapy. Another application is evaluating for suspected vascular graft infections. However, a positive FDG-PET must be interpreted with caution because prosthetic grafts have been noted to induce chronic inflammation and occasionally thrombosis, which results in increased FDG uptake in the absence of infection.

ENDOCARDITIS

Cardiac PET is increasingly being used to manage cases of suspected infective endocarditis (IE). Despite advances in imaging and microbiological testing, the diagnosis of IE remains a challenge in some cases, such as patients with implantable pacemakers, defibrillators, and prosthetic valves. It is important to note that the increased use of implantable cardiac devices and prostheses is changing the epidemiological profile of IE; for example, the incidence of staphylococcal and nosocomial cases have increased while the frequency of oral streptococcal endocarditis has decreased.[24]

The most recent effort to study the epidemiology of endocarditis comes from the European Infective Endocarditis Registry, a multicenter multinational cohort of 3,116 adults

admitted with suspected IE. For these patients, transthoracic echocardiography (TTE) was the first-line imaging modality for diagnosis, whereas transesophageal echocardiography was most commonly used in patients with suspected prosthetic valve endocarditis to assess for secondary complications such as pseudoaneurysm formation, periprosthetic abscess, and valve dehiscence, all of which are challenging on TTE. Other imaging modalities such as computed tomography angiography and CMR are also being used. One of the main findings of this registry was the increasing use of FDG-PET to establish a diagnosis in a significant number of patients. FDG-PET was performed in 518 patients (16.6%) and was more frequently used in those with prosthetic IE (25%) and cardiac device-related IE (26%) than in native valve endocarditis (9.5%). The accuracy of FDG-PET ranged from 67% in prosthetic valve IE to 28% in native valve endocarditis and 16% in cardiac device-related IE.[25]

As previously noted, patient preparation is key to the success of any cardiac PET imaging. For FDG-PET imaging in patients with suspected IE, the patient is instructed to follow a low-carbohydrate diet in the 24 hours preceding the scan with at least a 12-hour fast thereafter. This is imperative to ensure suppression of physiological myocardial glucose uptake. Inflammatory cells (leukocytes and macrophages) preferentially uptake glucose as their energy source, so the FDG is trapped in those cells because it cannot undergo glycolysis. This serves as the premise of inflammatory imaging. The use of 50 IU/kg heparin 1 hour prior to injection of FDG enhances glucose/FGD uptake. Patients are imaged for 10 to 20 minutes, and the data is interpreted by fusing/superimposing the PET and CT images. Any area of FDG uptake is an area of concern for active inflammation versus infection.

Adding PET to the modified Duke Criteria for assessing IE increases the diagnostic sensitivity from 70% to 97% ($P = .008$).[26] A meta-analysis of studies evaluating the diagnostic accuracy of FDG-PET for endocarditis suggests that there is a pooled sensitivity and specificity of 81% and 85%, respectively.[27] Similar rates have been reported for the diagnosis of cardiac device-related IE as well as left ventricular assist device infections. In both groups, the presence of extensive infection detected by cardiac PET has been associated with worse outcomes.[28]

The main limitation of using FDG-PET to diagnose endocarditis is the high false-positive rate, which reaches almost 15% in certain clinical scenarios.[29] Some studies advocate the use of FDG-PET coupled with a tagged white blood cell scan since the high specificity can improve diagnostic accuracy.[30] In a study by Calais and colleagues, 48 patients with suspected device infection were tested with both FDG-PET/CT and white blood cell single photon emission CT/CT. For FDG-PET/CT, the diagnostic sensitivity, specificity, and positive/negative predictive values were 80%, 91%, 80%, and 91%, respectively, versus 60%, 100%, 100%, and 85% for white blood cell single photon emission.[30] Prosthetic valve thrombosis can be associated with FDG uptake, which results in a diagnostic dilemma as it can be indistinguishable from prosthetic valve IE.[31] Early postoperative inflammatory changes can also lead to increased FDG uptake and result in a false-positive diagnosis of prosthetic valve IE or graft infection. To date, the timeframe for postoperative healing is still unclear and requires further research.[32]

CONCLUSION

Cardiac PET is a versatile modality that assists in clinical decision making for some of the most complex cardiovascular cases, including patients with ischemic heart disease, inflammatory cardiomyopathies, and those who have extensive, unrevealing, or equivocal workups.

KEY POINTS

- Cardiac positron emission tomography (PET) is a sensitive test to assess for myocardial viability. The presence of a mismatch defect is associated with significant improvement in left ventricular function post revascularization.
- Fluorodeoxyglucose (FDG)-PET is increasingly being used in the assessment of sarcoidosis. The presence of FDG uptake in an area of perfusion defect suggests active inflammation.
- Adding FDG-PET to the current criteria for diagnosing endocarditis improves diagnostic accuracy. This is primarily seen in prosthetic valve and cardiac device-related endocarditis.

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

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viability, positron emission tomography, endocarditis, inflammation, sarcoidosis

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