# The Role of PET/CT in the Diagnosis of Infective Endocarditis

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## Introduction

Infectious Endocarditis (IE) is a serious disease with high mortality rate (30–50%). It remains a diagnostic challenge due to its variable clinical presentation, spectrum of the microorganisms involved, the intrinsic characteristics of the patients and the increasing use of prosthetic materials and Intracardiac Devices (ICDs).[1] Approximately 20% of patients with IE have valvular prostheses or ICD,[2] and early diagnosis is essential, as delayed or inadequate treatment may lead to serious consequences, such as extensive perivalvular structural damage and systemic complications, worsening patient outcomes and increasing the risk of recurrence.[1]

According to the modified Duke criteria, which are the pillars used for diagnosis, definitive IE is mainly based on positive blood cultures with typical microorganisms and/or evidence of IE on echocardiogram. However, despite continuous progress in echocardiographic images and microbiology techniques, diagnosis of Prosthetic Valve Endocarditis (PVE) and ICD remains challenging, mainly because echocardiography and blood cultures are inconclusive in more than 20% of the cases, especially at the stages of the disease.[1]

In patients with high rates of suspicion, normal/inconclusive echocardiogram does not rule out diagnosis, generating a significant rate of indefinite cases. To improve the accuracy of the Duke criteria, other imaging scans, such as multiview Computed Tomography (CT), positron emission tomography with 18F-fluorodeoxyglucose and Single Photon Emission Computed Tomography (SPECT) have gained prominence.

## PET/CT: method and interpretation of results

Positron Emission Tomography (PET) combined with CT scan, or PET/CT, is an imaging method that associates information on (functional) metabolism with anatomical information. This allows to acquire fusion images and more accurate location of the lesion or abnormality investigated. This method is of great importance in Oncology, for diagnosis, staging and follow-up of treatment of multiple neoplasms. The main radiopharmaceutical drug used is fluorodeoxyglucose, which is a glucose analog and consequently a marker of metabolism, linked to Fluor 18 (F18-FDG). PET/CT with F18-FDG is also used for the diagnosis of neurological diseases, such as dementias and, in Cardiology, for assessment of myocardial viability, the investigation of cardiac sarcoidosis and, more recently, for the evaluation of patients with suspected IE not confirmed by other methods.

Preparation for PET/CT scan for the evaluation of suspected IE is fundamental, so that the accuracy of the method can be maintained.[1] In physiological situations, the myocardium uses glucose and fatty acids as substrate. As the radiopharmaceutical drug used to perform the test is a glucose analog, physiological uptake of F18-FDG should be suppressed for proper evaluation. The purpose of the preparation is that the use of glucose by the myocardium can be reduced or suppressed, making fatty acids the main source of myocardial energy, to better evaluate any abnormality in the prosthesis, paravalvular annulus or ICD. Although there is no consensus on the standard protocol of preparation, suppression of myocardial FDG uptake is usually achieved through a fat-rich low-carbohydrate diet for 24 hours, followed by minimum fasting of 12 hours. Unfractionated heparin increases blood concentration of fatty acids. However, most centers do not use heparin in the routine of patient preparation.

After the injection of the radiopharmaceutical drug, the patient remains at rest for 60 minutes. Images are then obtained for the evaluation of radiopharmaceutical uptake foci in the prosthetic or ICD (implantable defibrillator, pacemaker or electrode leads) site. Whole-body images are particularly important for the diagnosis of septic embolism, often being the only evidence for the diagnosis of IE. Due to the physiological brain uptake of FDG, PET/CT with F18-FDG is not suitable for the evaluation of cerebral septal embolism. Magnetic resonance imaging is the method of choice for this clinical scenario. Mean radiation dose is 5 to 15 mSv.

Interpretation of the images is performed by visual and quantitative analyses.[1] In the visual analysis, uptake of the radiopharmaceutical drug in the myocardium adjacent to the valve and the artifacts caused by the presence of metallic material of the valve prostheses should be considered. Different patterns of focal or diffuse perivalvar uptake may be observed, with varying intensities, and the duration of antibiotic therapy should be taken into account. To reduce variability in interpretation, it has been suggested to perform quantitative analysis using the same method used for the analysis of PET images in Oncology, called standard uptake value (maximum SUV), which depends on a series of variables, such as the amount of radiopharmaceutical drug injected and equipment characteristics, or the SUV ratio of the area of interest analyzed with the blood pool (SUV ratio). However, standardization of these values is not yet definitive.

### False positives

There are confounding factors that must be considered for

## Keywords

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an adequate interpretation of the test. The period between surgery and the test is important, since surgical trauma causes inflammatory effects that may lead to increased uptake of the radiopharmaceutical drug and, consequently, a false positive. However, there is no consensus on the ideal postoperative time to reduce the chances of a false positive, and some authors suggest a minimum period of 3 months. Inadequate suppression of the physiological uptake of FDG may also lead to false positive findings. Processing errors in the fusion of PET and CT images, as well as patient's movement during image acquisition, may also lead to misinterpretations.

### False negatives

On the other hand, long antibiotic therapies (lasting longer than 2 weeks) may reduce inflammatory response, causing false negatives. Small highly mobile vegetation may not be viewed on PET/CT due to the limitations of equipment spatial resolution. Very fibrous vegetations that isolate the germ causing the infection and consequently inflammatory response may not present hyperuptake of F18-FDG.

## Clinical Value of PET/CT in Infectious Endocarditis

In one of the first relevant studies on the subject, Pizzi et al.[2] evaluated 92 patients with suspected PVE or ICD. The authors demonstrated that the addition of PET/CT results to the modified Duke criteria and echocardiogram results allowed a review of the cases classified as potential IE in 90% of them, and allowed a conclusive diagnosis in 95% of the cases. In addition, there was a significant increase in diagnostic accuracy using PET/CT. The inclusion of CT with angiography added higher diagnostic value to PET/CT. The same author recently demonstrated an increase in diagnostic accuracy using PET/CT in adult patients with congenital heart disease and suspected IE or cardiac device infection using the modified Duke criteria.[3] There are some confounding factors that may affect the accuracy of the method for the diagnosis of IE. Swart et al.[4]evaluated the accuracy of PET/CT for diagnosis of IE in 160 patients with valve prosthesis. The study included a negative control group of 77 patients with valve prosthesis who underwent PET/CT with F18-FDG for another indication. When confounding factors were controlled excluding patients with low inflammatory activity, defined as CRP<40 mg/L (for example, secondary to prolonged use of antibiotics) and use of surgical adhesives, sensitivity, specificity and positive and negative predictive values were 91%, 95%, 95% and 91%, respectively, by visual analysis. Semiquantitative analysis using valve/activity in the descending aorta >2 presented sensitivity of 100% and specificity of 91%. It should be noted that, in that study, recent surgery did not affect diagnostic accuracy.

Kouijzer et al.[5] analyzed the value of PET/CT with F18-FDG for the diagnosis of IE in native valves. It evaluated 88 patients with suspected IE. Of ten patients with defined diagnosis of IE according to the modified Duke criteria, only three patients had abnormal F18-FDG uptake. In patients who did not meet the IE criteria, 90% of the tests were normal. The authors concluded that although a negative result does not rule out IE, when PET/CT demonstrates radiopharmaceutical drug uptake, it may support the diagnosis of IE if there is suspicion according to the modified Duke criteria. Besides, this method may be useful in the detection of metastatic infection.

In reviewing the diagnostic value of 18F-FDG-PET/CT for the detection of peripheral embolism and secondary infectious foci in patients with infective endocarditis and ICD infections, Mikail et al.[6] found that the detection of extracardiac septic foci is crucial, affecting substantially the outcome and treatment of patients, enhancing the clinical usefulness of 18F-FDG-PET/CT in this clinical setting. The authors concluded that a multimodal approach, combining the high sensitivity of 18F-FDG-PET/CT with morphological image, seems promising.

In a systematic review and meta-analysis evaluating the diagnostic accuracy of PET/CT with F18-FDG for the diagnosis of IE, PET/CT sensitivity was 81%, specificity was 85% and there was a very good diagnostic accuracy with area under the ROC curve of 0.9.[7] The sensitivity and specificity of scintigraphy with labeled leukocytes was 86% and 97%, respectively, with excellent diagnostic accuracy, with an area under the ROC curve of 0.96. In this review and meta-analysis, scintigraphy with labeled leukocytes showed sensitivity similar to that of PET/CT and superior specificity — a finding that can be explained by the fact that this technique only demonstrates sites with infection, rather than inflammation, unlike PET/CT with F18-FDG. However, scintigraphy with labeled leukocytes requires handling of blood components and is a time-consuming technique, which can last up to 24 hours, unlike PET/CT, which lasts, on average, 2 hours.

Mahmood et al.,[8] in a recent meta-analysis, evaluated the accuracy of PET/CT in the evaluation of a potential endocarditis. They identified 13 studies involving 537 patients. Pooled PET/CT sensitivity for the diagnosis of IE was 76.8 and specificity was 77.9%. Accuracy was higher in VP endocarditis, with 80.5% sensitivity and 73.1% specificity. Additional extracardiac foci of infection were found in 17% of patients in whole-body PET/CT. The authors concluded that PET/CT is an adjunct diagnostic tool that is useful in the evaluation of challenging cases of IE, particularly in PVE. It also has the potential to detect clinically relevant extracardiac foci of infection, leading to more appropriate treatment regimens and surgical interventions.

Gomes et al.[9] studied the value of imaging in addition to echocardiography in patients selected by a previously proposed flowchart. Imaging techniques were compared against each other in 46 patients who received echocardiography (transesophageal and transthoracic echocardiography), multiple detector computed tomography (MDCTA) and F18-FDG-PET/CT. The authors observed 86% sensitivity for patients without prosthesis and 100% for patients with prosthesis, when echocardiogram, MDCTA and FDG-PET/CT were combined for the diagnosis of endocarditis/intracardiac device infection. Echocardiography performed better in evaluating vegetations, morphological abnormalities/valve dehiscence, septal defects and fistula formation. MDCTA presented better performance in the evaluation of abscesses and infection of the ventricular assist device. FDG-PET/CT presented better performance in the evaluation of ICD infection, extracardiac infectious foci and alternative diagnoses. The authors concluded

that echocardiography, MDCTA and FDG-PET/CT provide relevant diagnostic information, particularly in patients with intracardiac prosthetic material.

The use of PET/CT has been recently incorporated into the European guidelines for the management of IE.[10] The use of PET/CT is suggested when clinical suspicion is high for PVE or ICD, but there is no diagnostic definition with clinical evaluation and echocardiogram nor for the evaluation of septic embolism. In addition to assisting diagnostic confirmation when there is clinical suspicion without definition by other imaging methods, PET/CT with F18-FDG helps to rule out IE when the result is negative (Figures 1, 2 and 3). Factors that may cause false positives or false negatives, such as recent surgical procedure for the placement of valve prosthesis or ICD or use of antibiotic therapy for more than 2 weeks, should be taken into account. The use of PET/CT for evaluation of IE in native valves is limited. Few studies have analyzed the method in this clinical setting, demonstrating low sensitivity but good specificity for IE diagnosis. Due to the mobility of the native valve, and often because the vegetation is small, IE detection is impaired in these cases, as well as in the subacute stage of the disease. Therefore, a negative PET/CT result does not rule out IE, but a positive result may help when clinical suspicion is high, and other methods did not confirm the diagnosis. Whole-body evaluation also allows the detection of septic embolism.

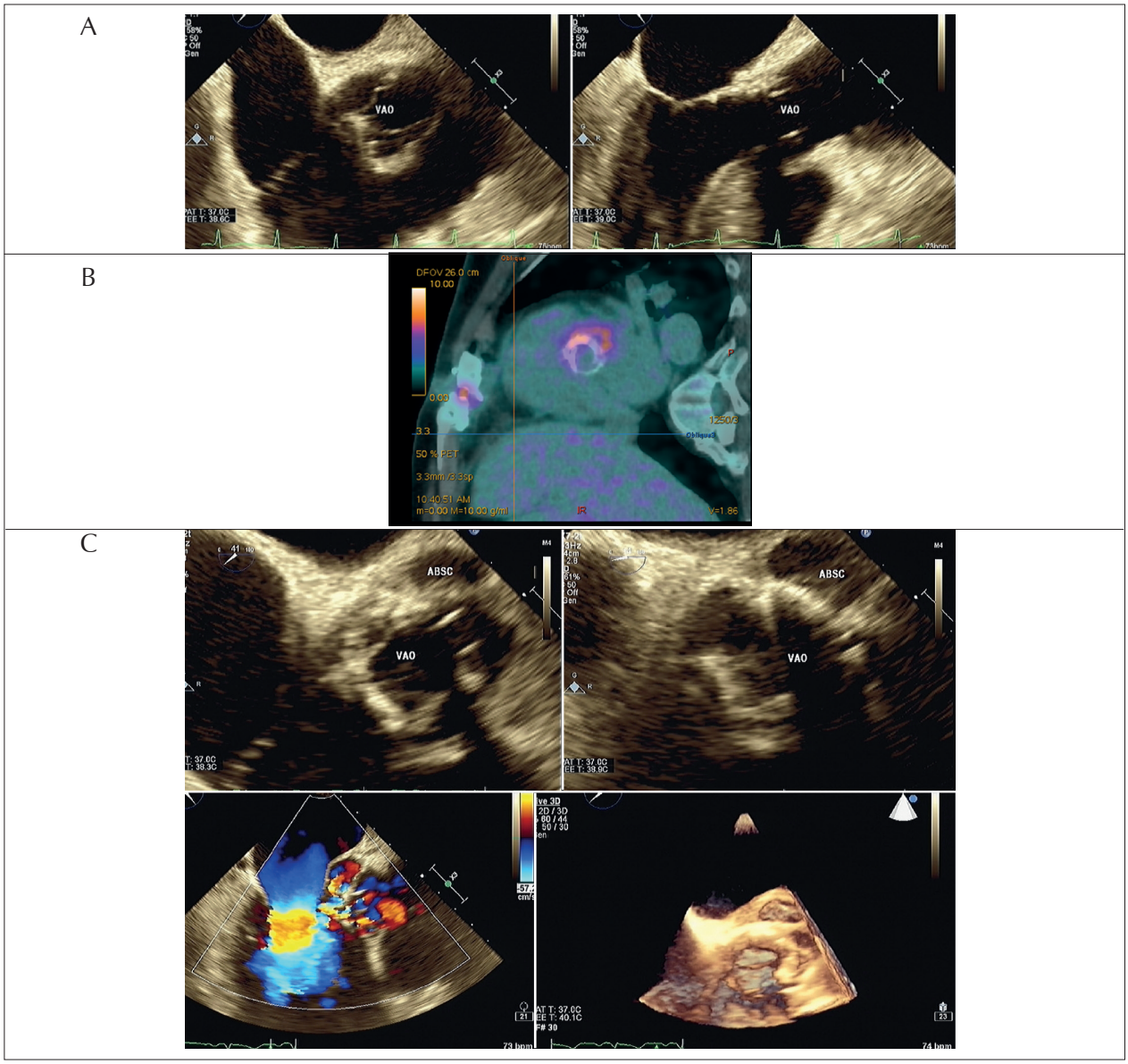


**Figure 1 –** *A 66-year-old male patient with a history of biological aortic prosthesis placed in 2003 and 2015, admitted with fever and suspected infective endocarditis in 2016. Initial echocardiogram showed no significant abnormalities (A). PET/CT with F18-FDG revealed perivalvar uptake of the radiopharmaceutical drug (B). Echocardiogram 1 month later revealed perivalvar abscess (C).*

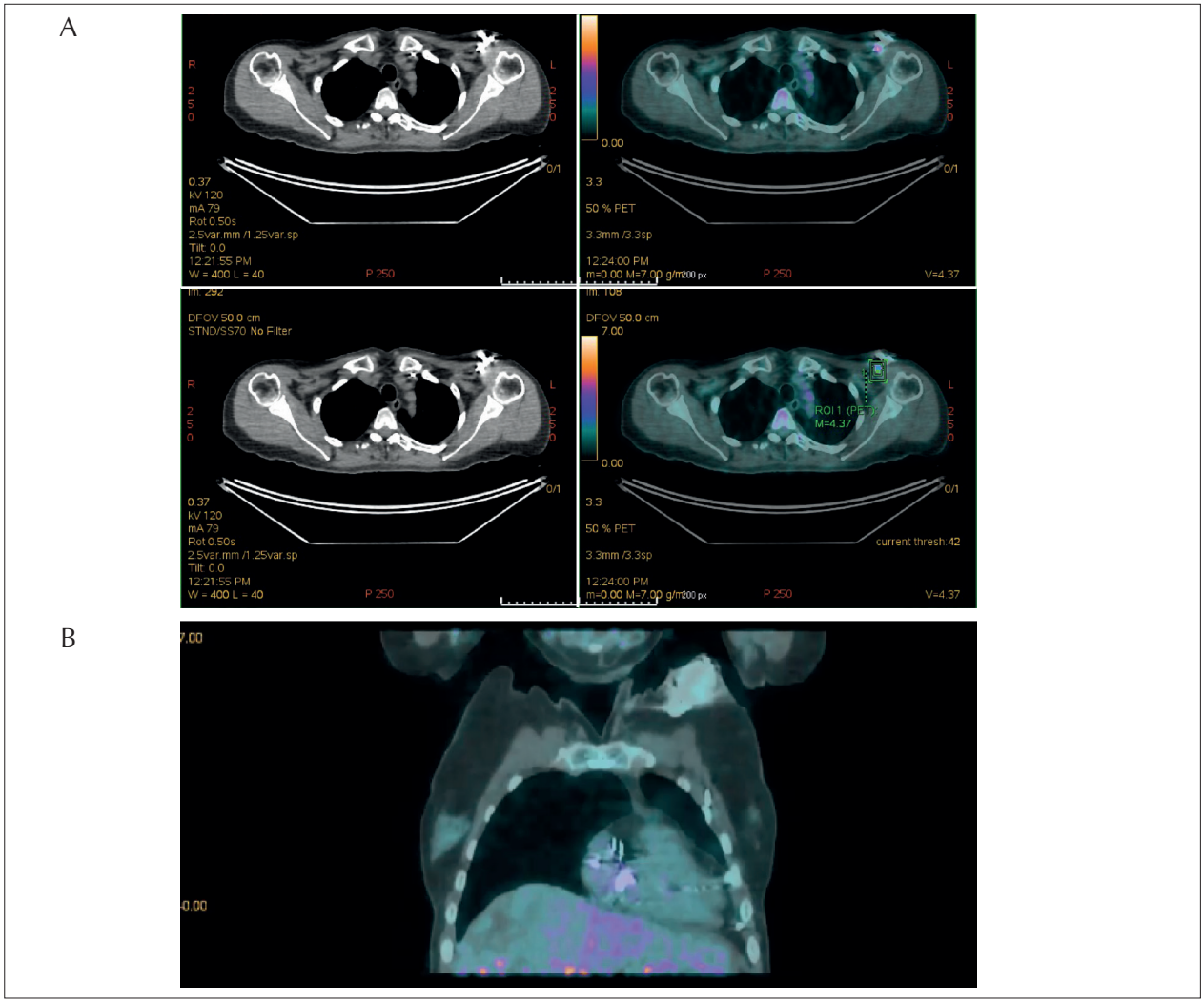


**Figure 2 –** *Male patient, 55 years old, diabetic, with tricuspid bioprosthesis and pacemaker with epicardial and transvenous leads. The patient showed clinical signs of pacemaker pocket infection. PET/CT with 18-FDG was performed to rule out pacemaker lead infection. Increased uptake of F18-FDG was observed in the pacemaker pocket, confirming the diagnosis of local infection (A). Pacemaker leads did not present any uptake, hence ruling out lead infection diagnosis (B).*

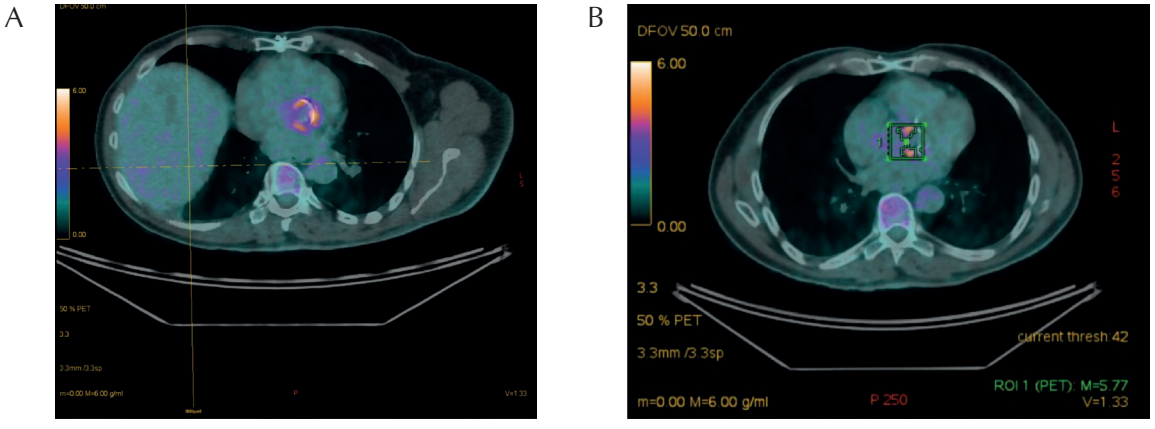


**Figura 3 –** *Male patient, 68 years old, with biological aortic prosthesis and history of fever and sweating, and normal transesophageal echocardiogram. (A) PET/CT with F18-FDG demonstrated perivalvar uptake of the radiopharmaceutical drug (B) Quantitative analysis demonstrated SUV of 5.77.*

## Conclusion

The incorporation of PET/CT in the evaluation of patients with suspected Infective Endocarditis has a well-defined niche. This diagnostic method should be used when there is high clinical suspicion without diagnostic confirmation with conventional methods in patients with valve prosthesis or intracardiac device, and it is also useful in the evaluation of septic embolism.

## Authors' contributions

Research creation and design: Grossman G. Data acquisition: Grossman G. e Carreira L. Manuscript writing: Grossman G. e Carreira L. Critical revision of the manuscript for important intellectual content: Grossman G. e Carreira L.

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