Review Article

My Approach To Nuclear Medicine in the Evaluation of Prosthetic Valve and Cardiac Implantable Electronic Device Endocarditis

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Summary

Nuclear medicine has played an increasing role in the evaluation of patients with a suspected or confirmed diagnosis of infective endocarditis. Scintigraphy with marked leukocytes (ML) is a method widely used in clinical practice to detect sites of infection, being especially indicated in patients with suspected infective endocarditis (IE) in prosthetic valves or implantable cardiac devices (ICD) when other conventional imaging methods studies are not conclusive. The technique involves labeling the patient's own leukocytes with a radiotracer, such as 99m Tc-HMPAO, maintaining its biological properties. Upon injection into the bloodstream, leukocytes actively mark sites of active inflammation, allowing detection of infection.

Blood collection for ML scintigraphy requires a sufficient amount of leukocytes, which can be a major limiting factor in patients with neutropenia. Another point of limitation is that the leukocyte labeling process and the start of obtaining scintigraphic images can take about 2 hours. The images are acquired at different times, and the presence of capture in the 4-hour and 24-hour images is important to confirm the presence of active infection.

ML scintigraphy has been recommended as part of the diagnostic algorithm for IE in patients with prosthetic valves or implantable cardiac devices such as pacemakers who suspect the disease, being considered a major modified Duke criterion when positive. It is indicated when the echocardiogram is inconclusive or doubtful, and may change the categorization of IE from possible to defined in up to 25% of patients. In addition, it can also be used in the investigation of embolic events in extracardiac sites, such as the lung, spleen and bone/joint tissue.

Positron Emission Tomography coupled with Computed Tomography (PET-CT) is a molecular imaging technique that has shown great importance in the management of IE. PET-CT uses a radiopharmaceutical labeled with a short-lived radioactive substance, such as 18F-fluordeoxyglucose (18F-FDG), which is captured by cells with high metabolism, such as inflammatory cells present in areas of active infection. This allows for accurate, non-invasive detection of areas of inflammation, including the lesions, vegetations and abscesses associated with IE.

The use of PET-CT in IE has shown promise in the early detection of infection, providing important information for diagnosis and treatment planning. Additionally, PET-CT can help differentiate between active infection and post-surgical complications, as well as identify areas of infection in extracardiac sites, which can be useful in evaluating more complex cases. The high sensitivity and specificity of PET-CT in detecting active inflammation make it a valuable tool in the clinical management of IE, especially in cases of moderate clinical suspicion or when conventional imaging methods are inconclusive. However, it is important to consider the limitations of PET-CT, such as its availability in some health centers, cost and exposure to ionizing radiation, and to use PET-CT findings in conjunction with other clinical and laboratory data for an proper diagnosis and management of IE.

Keywords

Endocarditis; Valve Prostheses and Implantable Electronic Heart Devices; PET-CT; Scintigraphy; Echocardiography

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Introduction

The incidence of infective endocarditis (IE) has been increasing. It is estimated to be 3-15 cases per 100,000 inhabitants per year and associated with elevated morbidity and mortality. The most common cause of IE is Staphylococcus aureus infection, affecting mostly male and older individuals. In the United States and Europe, 16-30% of all cases of IC are prosthetic valve (PV) endocarditis, and 25-35% of native valve endocarditis are acquired in the hospital. In Brazil, rheumatic valve disease is still an important predisposing factor for infection, in contrast with developed countries where rheumatic disease has become rare.[1]

Difficulty in raising clinical suspicion and confirming the diagnosis of IE are among the greatest challenges faced by cardiologists in their clinical practice. Although the use of clinical rules such as the Duke criteria increases the success of IE diagnosis and its clinical management, the presence of infection by atypical organisms, PVs or cardiac implantable electronic devices (CIEDs) can make the diagnosis of IE difficult.[1,2]

Risk factors for IE

The major risk factors for IE are congenital heart disease (CHD), previous episode of IE, and the presence of PV or

CIED.[1] Regarding CHDs, the incidence of post-surgical IE varies from 1.3 to 13.3%, in addition to the high risk of mortality for CHDs, estimated at 6-14%.[3] Recurrence or reinfection occurs in 2.6-8.8% of patients who survived IE, with high rates of complications and mortality.[1]

Epidemiology of IE in patients with PVs

Patients with PVs are at higher risk of IE in the first year after valve replacement, and the risk gradually decreases to a low and stable risk. Bioprosthetic valves are associated with a higher risk of IE as compared with mechanical valves. Besides, the risk of transcatheter aortic valve implantation (TAVI) for IE seems not to differ from that found in conventional surgery, with an incidence of 1.4-2.8 per 100 patient-years in the first year and 0.8 in each of the four following years.[2-4]

CIED-related IE corresponds to nearly 10% of the IE episodes.[1] In these cases, in-hospital mortality varies from six to 14%, with an overall mortality of approximately 20% a year.[5] PV endocarditis is a severe, life-threatening condition, accounting for 10-30% of all cases of IE, with an incidence of 0.3-1.2% per patient-year. Patients with PVs are considered to be at high risk for IE, with higher morbidity and mortality, often requiring surgical interventions, with associated risks.

Challenges in the management of IE in PVs and CIEDs

Echocardiography and laboratory tests are still the basis of diagnostic investigation of IE. However, conventional imaging techniques still yield inconclusive results in up to 40% of patients with PVs or CIEDs.[6] Transesophageal echocardiography (TEE) should be considered in all suspected cases of PV endocarditis for assessment of valve hemodynamics, and detection of vegetations, abscesses or fistulas. Detection of vegetation may be extremely difficult due to artifacts related to the material used in the PVs. Sensitivity of TEE in detecting IE in PVs varies from 82% to 96%, in contrast to transthoracic echocardiogram that has a sensitivity of 17-36%.[6] In case of suspicion of CIED endocarditis, echocardiography is the first test to be considered for detection of vegetations in the electrodes and cardiac valves, with TEE being superior to transthoracic echocardiography. Both techniques, however, have similar limitations for the detection of IE, be it for the size and location of vegetations, be it for the presence of foreign material to the body limits the visibility of echocardiogram. It is important to highlight that a normal echocardiogram does not rule out the diagnosis of IE in patients with CIEDs and clinical suspicion of IE.[7]

In light of the increasing number of cases of IE, its high morbidity and mortality, and diagnostic limitations of conventional techniques, studies investigating the usefulness of nuclear imaging techniques, including the 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET-CT) for in diagnosis of IE have been conducted. These techniques showed good cost-effectiveness relationship, preventing prolonged hospitalizations and unnecessary studies, and improving patient clinical outcomes. The set of studies in the literature, including meta-analysis and systematic reviews have demonstrated the clinical impact of 18F-FDG PET/CT, supporting its inclusion in the European guidelines on the investigation of PV endocarditis since 2015[1] and in the North American guidelines since 2020.[8] In addition to PET-CT, another useful alternative is labeled leukocyte scintigraphy (LLS), currently the gold-standard method in the investigation of infections of prosthetic orthopedic implants. The method is also specific for IE, and useful in confirming the diagnosis in case of possible false-positive PET-CT results, as in the first months after surgery.[1,9-11]

How to use PET-CT in IE

The main use of PET-CT in the management of IE is in patients with suspicion of PV or CIED endocarditis, whose results from transthoracic or transesophageal echocardiogram were inconclusive or negative. In 18F-FDG PET/CT, FDG uptake occurs in areas of increased metabolic activity, since 18-fluorine is intensively captured by inflammatory cells. Thus, accumulation of the marker around the PV or in perivalvular cardiac tissues is a powerful indicator of active infection. Besides, whole-body 18F-FDG PET-CT allows the detection of infectious complications of endocarditis, such as splenic embolization, embolism to the lower extremities, spondylodiscitis, or even the portal entry in case of infection of soft tissues or the oral cavity.

The study supporting the inclusion of PET-CT in the European Society of Cardiology guidelines was the study by Saby et al.[12] The authors prospectively studied 72 consecutive patients with PV endocarditis, who were subjected to clinical, microbiological, and echocardiographic evaluation. Thirty-six patients (50%) exhibited abnormal FDG uptake around the site of the PV. The sensitivity, specificity, positive predictive value, negative predictive value, and global accuracy were as follows (95% confidence interval): 73% (54% to 87%), 80% (56% to 93%), 85% (64% to 95%), 67% (45% to 84%), and 76% (63% to 86%), respectively. Adding abnormal FDG uptake around the PV significantly increased the sensitivity of the modified Duke criteria at admission (70% [52% to 83%] vs. 97% [83% to 99%] and became a new major criterion for IE diagnosis. This study was crucial in demonstrating the usefulness of 18F-FDG PET-CT in diagnosing IE in patients with PV.[12] In 2015, the ESC included the 18F-FDG PET-CT in the algorithm for the detection of VP endocarditis as a major diagnostic criterion (Figure 1). PET CT should be carried out in patients whose modified Duke criteria are inconclusive (possible or rejected IE, in the presence of high clinical suspicion), two months after cardiac surgery, due to the risk of false-positive results related to scarring inflammatory process. At this point, the exam of choice is 18F-FDG PET-CT with labeled leukocytes.[1] In Figure 2, we illustrate the use of 18F-FDG PET-CT in a patient with suspected IE and persistently negative echocardiography despite positive blood cultures. PET-CT clearly demonstrated abnormal glycolytic metabolism in the aortic prosthesis that was subcutaneously implanted on a valve-tube graft (valve-in-valve), compatible with IE.

It is worth noting that PET CT has also been indicated for patients with suspected IE in native valves and even for patients with confirmed IE, for localization of both local (e.g. cardiac abscesses) and distal (e.g. septic embolism) complications. This has been compiled in the literature by systematic

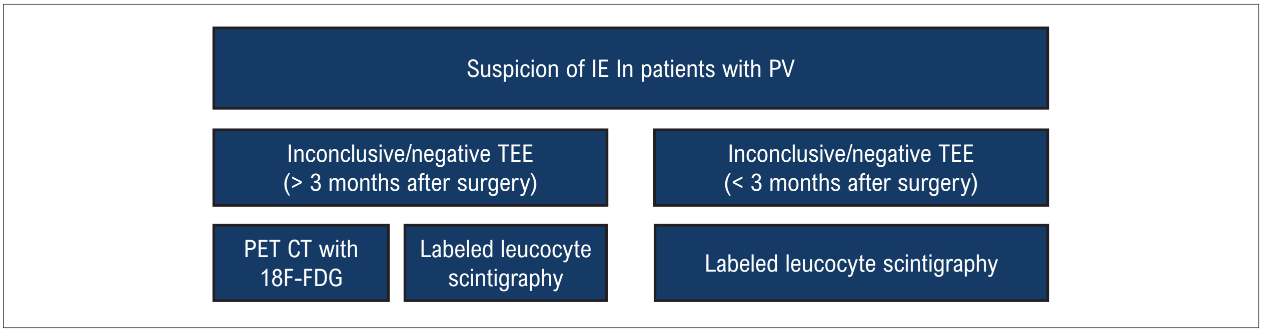

Figure 1 – *Patients with suspected PV endocarditis benefit from the use of nuclear medicine after echocardiographic investigation, particularly TEE (adapted from Habib et al.1). IE: infective endocarditis; TEE: transesophageal echocardiography, 18F-FDG PET-CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; PV: prosthetic valve*

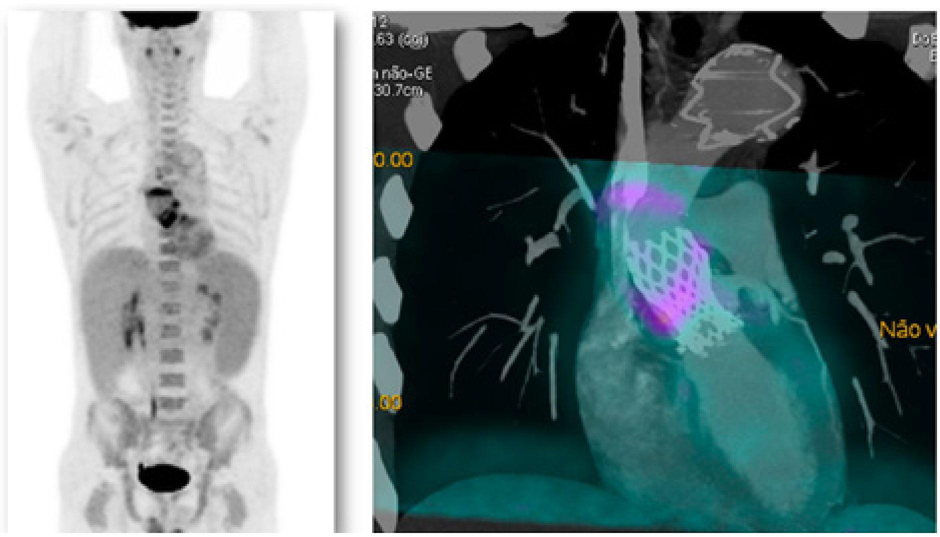

Figura 2 - *PET CT with 18F-FDG showing tracer uptake around valve endoprosthesis (valve-in-valve transcatheter aortic valve replacement) in a patient with positive blood cultures for streptococcus and persistently negative transesophageal echocardiograph; positive PET CT scan for IE*

reviews and meta-analyses, and been recommended by guidelines, including the updated Brazilian guideline on nuclear cardiology, updated in 2020.[13] The use of PET-CT in the assessment of cardiac inflammation is one of the branches of nuclear medicine in precision medicine, not only in IE but also in the evaluation of myocarditis, particularly cardiac sarcoidosis, and pericardial inflammation.[14]

When to use LLS in the management of IE in PVs and CIEDs

LLS has been widely used to detect infection sites and applied in clinical practice for decades. Today, its use is recommended in patients with suspected IE, particularly in those with PVs or CIEDs, with negative results from conventional imaging methods but still with moderate/high suspicion of IE. In LLS, patient blood is aseptically prepared for labeling of leukocytes with a radiotracer, such as the ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO). The leukocytes are then radiolabeled, without losing their biological properties of chemotaxis and diapedesis, *i.e.*, they can actively accumulate in active inflammation sites after being injected into the circulation.

In this method, a sufficient number of leukocytes is required; 50mL of blood is collected from the patient, and for neutropenic individuals ($<2x10^3$ neutrophils/mm^3), an additional sample of blood may be required. Thus, the presence of neutropenia may be a limitation for the test. Also, LLS takes longer than 18F-FDG PET/CT, due to the whole process of labeling of leukocytes, and plasma and leukocyte isolation, which may take approximately two hours. For IE investigation, scintigraphic images are acquired at four and 24 hours after injection. This is important, since the scintigraphic criteria for detecting active infection is the presence of radiolabeled leukocyte uptake at four hours and an increase of the uptake at 24 hours. If radiolabeled leukocyte uptake is detected at four hours but not at 24 hours, the scans are classified as negative.[2] The type of scintigraphic imaging is also important. In addition to the conventional whole-body and static images of the region of interest (*i.e.,* the chest), single photon emission computerized tomography (SPECT) images are also indispensable in the investigation of endocarditis. Hybrid CT/scintigraphy devices allow acquisition of SPECT-CT images, which are more sensitive and specific than conventional scintigraphy and important in the diagnosis of IE (Figure 3).

99mTc-HMPAO-labeled leukocytes has several indications, including in IE investigation. In 2015, the method was formally included in the ESC guidelines in the diagnostic algorithm of IE in patients with PV or CIED and suspected IE, as a major modified Duke criterion.[1] According to the guidelines, ^{99m}Tc-HMPAO-labeled leukocytes is indicated for patients with suspected IE, when echocardiographic findings are inconclusive or doubtful, as it can change patient classification from possible IE (by the Duke criteria) to definite IE in up to 25% of cases. The method is also indicated for detection of embolic events in extracardiac sites. Scintigraphic findings of embolic disease/metastatic infection in the lungs, spleen, bone and articular tissue.[6] For the investigation of PV endocarditis, scintigraphy combined with ^{99}mTc-HMPAO-labeled leukocyte SPECT-CT has a sensitivity of 86% and specificity of 97%.[15] Sensitivity of this method can reach 100% with the presence of perivalvular abscess.[5] For CIED-associated IE, scintigraphy with ^{99}mTc-HMPAO-labeled leukocyte SPECT-CT had 94% sensitivity, 100% specificity, 100% positive predictive value and 94% negative predictive value.[16] Besides, in these cases, the method helps to describe the extension of the infection, and whether it was specific to the generator or if the cables were involved. Patients with positive scintigraphy have higher risk of in-hospital mortality and complications.[8] The literature recommends 18F-FDG PET-CT as the first line imaging modality due to its higher sensitivity compared with scintigraphy. Scintigraphy has higher specificity and is particularly useful for patients with a history of recent surgery (within the last two months) due to higher chance of false-positive 18F-FDG PET-CT.[17]

One of the greatest advantages of LLS is its high specificity for IE related to PV or devices, especially when compared with 18F-FDG PET-CT, and the earlier screening for IE in patients with recent surgery compared with PET-CT. Also, as compared with 18F-FDG PET-CT, there is no need for a special diet or fasting. Another advantage is the test is covered by the Brazilian national agency for supplementary health, which is not true for PET-CT.

Limitations for LLS in clinical practice include manipulation of patient's blood, the minimum volume of blood required for labeling, equipment (laminar flow cabinet and centrifuge) for leukocyte labeling). While in LLS, images should be obtained at two time points (four and 24 hours), in 18F-FDG PET-CT, 60- minute image acquisition was performed. Other clinical situations that may limit the use of LLS and its sensitivity are neutropenia, use of antibiotics or steroids, type of pathogens (higher sensitivity for neutrophil-mediated infections) and small vegetations (<6mm).[6]

Finally, similar to PET-CT, LLS uses ionizing radiation, which, *per se*, is contraindicated in pregnancy. Lactating women should be instructed to discontinue breastfeeding for 24 hours mainly due to exposure of the infants to radiation while on their laps.

Comparison of 18F-FDG PET CT *versus* LLS

How to choose a nuclear imaging technique when both 18F-FDG PET CT and LLS are available? Referral centers for patients with suspected IE should have both techniques available; the methods are complementary, especially in highly complex cases and recent surgeries. The decision on which method to use should be individualized for each patient. Factors like technical characteristics, costs and availability of the methods, expertise of the group, and patient severity should be considered. In general, 18F-FDG PET CT is the method of choice in the literature, considering its wide availability in first-world countries, where the factor "cost" is less relevant in light of such a lethal disease as IE.[18] What makes FDG PET CT scintigraphy the method of choice is its operational characteristics. Rouzet et al.[19] compared the performance of 18F-FDG PET and LLS in patients with PVs and showed that the former offers high sensitivity for the detection of active infection in patients with suspected

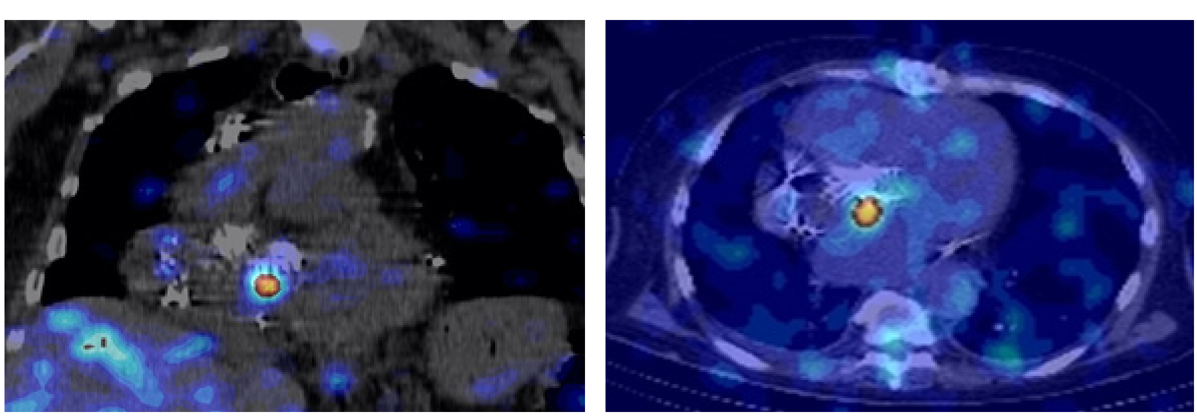

Figure 3 – *99mTc- HMPAO-labeled leukocyte scintigraphy with SPECT/CT in coronal (a) and axial (B) planes, with focal uptake in percutaneously inserted aortic valve prosthesis*

PV endocarditis and inconclusive echocardiography.[19] However, LLS offered a higher specificity than for diagnosis of IE and should, mainly in the first two months after cardiac surgery. A direct comparison of nuclear imaging techniques in patients with CIEDs was conducted by Calais et al.,[20] who compared 18F-FDG PET CT with LLS. Forty-eight patients underwent both 18F-FDG PET CT and LLS. The diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were respectively 80%, 91%, 80%, and 91% for 18F-FDG PET CT and 60%, 100%, 100%, and 85% for LLS. Although PET-CT was more sensitive than LLS, the latter showed higher specificity.[20]

Conclusions

Nuclear medicine has become part of the diagnostic investigation of IE in patients with PVs or CIEDs. 18F-FDG PET CT has high sensitivity for detecting active infection when echocardiographic findings are inconclusive or negative. LLS is more specific than18F-FDG PET CT for the diagnosis of IE and should be considered in cases of doubtful or suspected false-positive 18F-FDG PET CT or in the first two months after cardiac surgery.

Author Contributions

Conception and design of the research: Mesquita CT, Rezende MF; writing of the manuscript and critical revision of the manuscript for intellectual content: Mesquita CT, Rezende MF, Yahir DS, Palazzo IC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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