PET/CT Imaging in Devices Infective Endocarditis:

Ready for Prime Time

Running title: Lancellotti et al.; PET/CT in Infective Endocarditis

Patrizio Lancellotti, MD, PhD1,2; Gilbert Habib, MD, PhD3; Cécile Oury, PhD1; Alain Nchimi, MD, PhD1

1Department of Cardiology and Radiology, GIGA-Cardiovascular Sciences, University of Liège, Liège, Belgium; 2Gruppo Villa Maria Care and Research, E.S. Health Science Foundation, Lugo, Italy; 3Service de Cardiologie, C.H.U. De La Timone, Marseille, France

Address for Correspondence:
Patrizio Lancellotti, MD, PhD
Department of Cardiology
University of Liège Hospital
CHU Sart Tilman, Avenue de l’Hopital
1 B-4000 Liège Belgium
Tel: +32 4 366 7196
Fax: +32 4 366 7195
E-mail: plancellotti@chu.ulg.ac.be


Key words: Editorial, imaging, echocardiography
Over the last decade there has been a remarkable increase in prosthetic heart valve replacement and cardiac implantable electronic device utilization. Although capable of improving the quality and quantity of life of patients suffering from severe valvular heart disease or rhythm disorders, they are both subject to potentially life-threatening infection involving the endocardium, referred to as device infective endocarditis (DIE)\(^1,2\).

The rate of prosthetic valve endocarditis (PVE) ranges from 1–6% to 15%, being higher in revision surgery\(^1\). The infection usually involves the junction between the sewing ring and the annulus, leading to perivalvular abscess, dehiscence, pseudo-aneurysms, and fistulae, or the leaflets of the prosthesis, leading to vegetations, cusp rupture, and perforation. Cardiac device-related infective endocarditis (CDRIE), to be distinguished from local device infection (pocket/generator), is defined as an infection involving the electrode leads, cardiac valve leaflets, or endocardial surface. An incidence of 1.4 per 1000 device-years of definite CDRIE has been reported\(^3\). DIE may occur at anytime, being related to surgery only in early cases.

Under and over diagnosis of DIE can carry significant risk of death, considerable morbidity, unnecessary antimicrobial therapy, and excessive costs. The diagnostic approach of DIE does not differ from other forms of infective endocarditis, although it is more challenging. The diagnosis is definite in cases of typical pathological features obtained after device removal. In daily practice, the diagnosis of DIE relies on the modified Duke criteria that use typical clinical signs and symptoms and positive blood cultures to reach a definitive diagnosis when the device can be shown to be affected on echocardiography. This clinical approach yields a better sensitivity (70-80%) when these criteria are examined at the end of patient follow-up rather than in the early stage of the disease\(^4\). Addition of local signs of infection and pulmonary embolism as major clinical criteria also improves their sensitivity in case of suspected CDRIE\(^5\). The modified
Duke criteria has a lower diagnostic accuracy in DIE, for which echocardiography gives uncertain results in up to 15-30% of cases\textsuperscript{1,4}. Vegetation, abscess or pseudoaneurysm, and new PV dehiscence are major diagnostic Duke criteria for DIE. While transthoracic echocardiography (TTE) has relatively high specificity for detecting vegetations and abscesses (90%), its sensitivity lies between 40 and 80%. Transesophageal echocardiography (TEE) has better sensitivity for the diagnosis of both conditions (90%). Small PV abscesses are however more difficult to identify, particularly in the early post-operative period. TEE has also superior sensitivity and specificity to transthoracic echocardiography for the diagnosis of CDRIE.

Overall, the modified Duke criteria rely heavily on echocardiography, which is relatively insensitive in the early stage of the disease (morphological criteria) or maybe difficult to interpret in cases of PV (artefacts). In patients with high index of suspicion, a normal/inconclusive echocardiographic examination does not therefore rule out DIE, generating a significant rate of inconclusive diagnoses. For improving the accuracy of the Duke criteria, other imaging modalities such as multidetector computed tomography (MDCT), \textsuperscript{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have recently gained importance\textsuperscript{6-19}.

With the use of retrospective ECG-gated acquisitions and intravenous contrast to enhance vascular structures, current generation CT scanners provide enough spatial detail to visualize the valvular structures at several different phases of the cardiac cycle without motion artefact. The so-called cardiac CT angiography (CTA) is possibly superior to TEE for the evaluation of peri-valvular complications such as abscesses and pseudoaneurysms or fistulae. However, its negative predictive value to detect vegetations depends on their size (lesions \( \geq 5 \text{ mm} \); 100% negative predictive value if \( > 1 \text{ cm} \) vs. 55% if \( <1 \text{ cm} \)). Overall, its diagnostic accuracy is similar to TEE.
for vegetation and new PV dehiscence, but remains lower for leaflet perforation\textsuperscript{6,7}. On the other hand, the ability of MDCT to assess the entire chest (identification of septic pulmonary infarcts and abscesses), and adjacent cardiothoracic structures, such as the aorta, vena cava and coronary arteries can also be invaluable to diagnosing clinical problems and management planning\textsuperscript{8}.

The shortcomings of the diagnosis of DIE based on morphological changes have triggered an increasing use of SPECT and PET for the evaluation of the increased metabolic activity caused by the infection, prior to any structural change. The integration of the anatomic detail provided by unenhanced CT with metabolic imaging (SPECT/CT and PET/CT) has improved the accuracy and utility of this approach. Several reports have highlighted the potential added value of SPECT/CT imaging of radiolabelled leukocytes and \textsuperscript{18}F-FDG PET/CT in the diagnosis of DIE in patients with a negative or inconclusive routine work-up with TTE and TEE\textsuperscript{9-19} (Table 1). Radiolabelled leukocyte SPECT/CT imaging seems to be more specific for the detection of infective endocarditis and infectious foci than \textsuperscript{18}F-FDG PET/CT. However, the latter is likely the preferred imaging technique since SPECT/CT is less sensitive, more time consuming and require leukocyte labelling\textsuperscript{1,16}. \textsuperscript{18}F-FDG is a glucose analogue used to identify areas of infection and regions of vascular inflammation by highlighting cells with higher metabolic activity such as activated leukocytes, monocyte-macrophages, and CD4+ T-lymphocytes. In a recent prospective study, Saby et al. showed that adding abnormal FDG uptake around a PV to the modified Duke criteria at admission increased the sensitivity for the diagnosis of PVE from 70\% to 97\%\textsuperscript{15}. This result was due to a significant reduction in the number of possible PVE cases from 56\% to 32\%. Similar data have been reported in CDRIE with the possibility of assessing the extension of the infectious process and differentiating between DIE and other post-implantation phenomena (e.g., pocket hematoma, inflammation)\textsuperscript{9-14}. 
Interestingly, several reports showed that FDG-PET/CT could detect clinically unsuspected sites of extracardiac infection in up to 10-28% of cases\textsuperscript{18,19}.

In this issue of Circulation, Pizzi et al. evaluated the incremental value of \textsuperscript{18}F-FDG-PET imaging in association with CT(A) over the modified Duke score at admission for the diagnosis of infective endocarditis in 75 patients with PV or cardiac devices (mostly cardiac implantable electronic devices)\textsuperscript{17}. PET/CTA acquisitions were classified as positive or negative. After ≥3-month follow-up, each patient was classified by an expert team with a diagnosis of definite, possible or excluded DIE. The authors found that PET/CTA offered an excellent diagnostic performance (sensitivity 87%, specificity 90%) for the detection of DIE. PET/CTA in association with Duke criteria allowed reclassifying 90% (35/39) of cases initially classified as “possible” IE and provided a more conclusive diagnosis (definite/reject) in 95% (71/75) of cases. Besides, PET/CTA identified a greater number of anatomic lesions than PET/CT (sensitivity 91% versus 86.4%), many of them relevant for clinical and surgical decision-making (pseudoaneurysms, fistulas, thrombosis and coronary involvement). Furthermore, PET/CTA also detected more peri-annular complications than echocardiography, highlighting the difficulty of echocardiographic evaluation in these patients and the benefit of CTA as a valuable alternative.

Interestingly, the diagnostic accuracy of PET/CTA was pretty similar in PV and intracardiac devices. The quantitative analysis of FDG uptake was discriminant in PVE, but not in intracardiac devices, maybe due to the higher rate of intracardiac lead infection. The authors also confirmed that PET/CT was capable of detecting distant embolic sites (15%), most of which were clinically silent, and previously undiagnosed tumors (6.5%), many of them in early stages and potentially curable.

This study confirms earlier promises and extends previous results showing that sizeable
benefits can be obtained by including PET/CT and particularly PET/CTA in the initial diagnostic workup of patients with suspected DIE and non-conclusive echocardiography when adopting accurate patient selection and inclusion criteria by an expert endocarditis team. The benefits of PET/CT(A) are mostly related to the early identification of endocardial involvements, better evaluation of perivavular lesions, and documentation of extracardiac complications (silent embolic events or metastatic infectious events) or associated features (i.e., neoplastic lesions) (Figure 1). Abnormal FDG (or radiolabelled leucocyte SPECT) uptake around PV and definite perivalvular lesions on cardiac CT are considered major Duke criteria in the 2015 European Society of Cardiology guidelines, whilst an embolic event detected by imaging only represents a minor criterion. A class IIb recommendation have been made for intracardiac devices.

Although, the study of Pizzi et al. provides further evidence, the limited number of patients with suspected CDRIE does not allow drawing more definite indications yet. Additional potential roles of PET/CT in DIE, though not yet proven, would be to monitor responses to antimicrobial treatment in patients with established DIE and to help in individual risk stratification. Nevertheless, further work is required to define the best quantitative FDG uptake thresholds that might be used to diagnose and follow DIE evolution. With regard to the PET signal contamination, important issues remain unsolved, such as the adaptation of the optimal patient preparation and image acquisition protocols (e.g., impact of hyperglycemia or leukopenia), physiological FDG uptake and nonspecific uptake by uninfected tissues (active thrombi, atherosclerotic plaques, vasculitis, foreign body reactions). Further developments should not only address these issues using for example more specific radionuclide probes or targets, but also those related to the detection of <5 mm vegetations (limit of resolution) and the radiation exposure. On clinical grounds, the use of intravenous contrast agents should be considered with
caution, especially in case of renal insufficiency or concomitant use of nephrotoxic medication such as certain antibiotics. The best timing of imaging relative to the intervention (post-operative inflammatory response with possible false positive responses), or the initiation of antimicrobial treatment (risk of false negative cases) remains unknown. Lastly, whether PET/CT(A) would contribute to shorten the hospital stay, prevent clinical complications and reduce the cost of hospitalization, also need to be elucidated.

**Conflict of Interest Disclosures:** None.

**References:**


17. Pizzi MN, MD, Roque A, Fernández-Hidalgo N, Cuéllar-Calabria H, Ferreira-González I,


Table 1. Role of $^{18}$F-FDG PET/CT in suspected device infective endocarditis.

<table>
<thead>
<tr>
<th>Authors (Years and Reference)</th>
<th>Population</th>
<th>Method</th>
<th>Site of infective endocarditis</th>
<th>Exclusion criteria</th>
<th>Final diagnosis</th>
<th>Duke Criteria</th>
<th>$^{18}$F-FDG PET results</th>
<th>Duke Criteria + $^{18}$F-FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bensimhon L et al. (2011; 9)</td>
<td>N=21 with suspected CIED infection + 14 controls</td>
<td>$^{18}$F-FDG PET/CT 15 under antibiotic treatment</td>
<td>Pacemaker</td>
<td>Not specified</td>
<td>Definite IE =10</td>
<td>Not specified</td>
<td>Generator</td>
<td>Sensitivity=80% Specificity=100% Leads</td>
</tr>
<tr>
<td>Sarrazin JF et al. (2012; 10)</td>
<td>N=42 with suspected CIED infection + 12 controls</td>
<td>$^{18}$F-FDG PET/CT 11 under antibiotic treatment</td>
<td>Pacemaker</td>
<td>Not specified</td>
<td>Definite IE =35</td>
<td>Not specified</td>
<td>Sensitivity=88.6% Specificity=85.7%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Cautela J et al. (2013; 11)</td>
<td>N=21 with CIED infection (13 with CDRIE)</td>
<td>$^{18}$F-FDG PET/CT 11 under antibiotic treatment</td>
<td>Pacemaker</td>
<td>Not specified</td>
<td>Definite IE =7</td>
<td>Not specified</td>
<td>Sensitivity=90.8% Specificity=62.9%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Leccisotti L et al. (2014; 12)</td>
<td>N=27 with suspected CIED infection +15 controls</td>
<td>$^{18}$F-FDG PET/CT 11 under antibiotic treatment</td>
<td>Pacemaker</td>
<td>Not specified</td>
<td>Definite IE =7</td>
<td>Not specified</td>
<td>Standard</td>
<td>Sensitivity=86% Specificity=100% Delayed</td>
</tr>
<tr>
<td>Graziosi M et al. (2014; 13)</td>
<td>N=27 with suspected CIED infection</td>
<td>$^{18}$F-FDG PET/CT</td>
<td>Pacemaker</td>
<td>Not specified</td>
<td>Definite IE =5</td>
<td>Not specified</td>
<td>Sensitivity=63% Specificity=86%</td>
<td>Reclassification of 48% of cases</td>
</tr>
<tr>
<td>Ahmed FZ et al. (2015; 14)</td>
<td>N=46 with suspected CIED infection + 40 controls</td>
<td>$^{18}$F-FDG PET/CT 6 weeks post-implantation</td>
<td>Pacemaker</td>
<td>Not specified</td>
<td>Definite PVE =20</td>
<td>Not specified</td>
<td>Sensitivity=97% Specificity=98%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Saby L et al. (2013; 15)</td>
<td>N=72 with suspected PVE</td>
<td>$^{18}$F-FDG PET/CT 15 under antibiotic treatment</td>
<td>44 Biological PV 28 Mechanical PV</td>
<td>Pregnancy Inability to lie flat Need for urgent cardiac surgery Hemodynamic instability Cardiac surgery &lt; 1 month Blood glucose level &gt; 1.8 g/l</td>
<td>Definite PVE =30 Possible PVE =22 Rejected PVE =20</td>
<td>Not specified</td>
<td>Sensitivity=70% Specificity=80%</td>
<td>Sensitivity=73% Specificity=80%</td>
</tr>
</tbody>
</table>

DOI: 10.1161/CIRCULATIONAHA.115.018521
<table>
<thead>
<tr>
<th>Study</th>
<th>N=</th>
<th>Technique</th>
<th>Findings</th>
<th>Clinical Presentation</th>
<th>Definite PVE</th>
<th>Possible PVE</th>
<th>Rejected PVE</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Reclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rouzet F et al (2014; 16)</td>
<td>39</td>
<td>¹⁸F-FDG PET/CT, Radiolabelled leucocyte SPECT/CT, 28 under antibiotic treatment</td>
<td>24 Biological PV, 13 Mechanical PV, 2 others</td>
<td>Stimulation device, Vascular prosthesis, Left ventricular assist device, Complicated PVE requiring immediate surgery.</td>
<td>14</td>
<td>4</td>
<td>21</td>
<td>93%</td>
<td>71%</td>
<td>46%</td>
</tr>
<tr>
<td>Pizzi MN et al. (2015; 17)</td>
<td>92</td>
<td>¹⁸F-FDG PET/CT(A), CTA in 76 cases, Median time 7 days, All under antibiotic treatment</td>
<td>40 Biological PV, 25 Mechanical PV, 25 Pacemaker, 11 Implantable defibrillator/resynchronizer, 10 others</td>
<td>Need for urgent cardiac surgery, Hemodynamic instability</td>
<td>52</td>
<td>5</td>
<td>35</td>
<td>51.3%</td>
<td>92%</td>
<td>90%</td>
</tr>
</tbody>
</table>

CIED: cardiac implantable electronic devices. Other abbreviations: see text.
Figure Legend:

**Figure 1.** Potential roles of PET/CT(A) in device infective endocarditis. Abbreviations: see text.
Suspicion of Device Infective Endocarditis*  

** TTE/TEE  

- Rejected  
- Possible  

High Index of Suspicion Negative/Inconclusive  

** PET/CT(A)**  

- Abnormal $^{18}$F-FDG uptake around the device***/at distance  
- Vegetation, Abscess, Pseudoaneurysm, Intracardiac fistula, New PV dehiscence  
- Embolic Events  

Definite  

Definite  

Definite  

Definite  

- Extension of the disease Risk Stratification Monitoring  
- Associated features (i.e., Neoplasia)  

** Includes PVE and CDRIE  
** Radiolabelled Leukocytes SPECT/CT can be used as an alternative  
***/ only after >3 months of implantation for PV and >6 weeks for other devices (i.e., pacemaker)