Editorial

Positron Emission Tomography/Computed Tomography Imaging in Device Infective Endocarditis

Ready for Prime Time

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Over the past decade there has been a remarkable increase in prosthetic heart valve replacement and cardiac implantable electronic device use. Although capable of improving the quality and quantity of life of patients who have 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]

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The rate of prosthetic valve (PV) endocarditis ranges from 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, pseudoaneurysms, 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.

Underdiagnosis and overdiagnosis 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] The addition of local signs of infection and pulmonary embolism as major clinical criteria also improves their sensitivity in the 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% to 30% of cases.[1,4] Vegetation, abscess or pseudoaneurysm, and new PV dehiscence are major diagnostic Duke criteria for DIE. Although transthoracic echocardiography 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 more difficult to identify, however, particularly in the early postoperative period. TEE also has sensitivity and specificity superior 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 may be difficult to interpret in cases of PV (artefacts). In patients with a 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 (CT), ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have recently gained importance.[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 artifact. The so-called cardiac CT angiography (CTA) is possibly superior to TEE for the evaluation of perivalvular complications such as abscesses and pseudoaneurysms or fistulae. However, its negative predictive value to detect vegetations depends on their size (lesions ≥ 5 mm; 100% negative predictive value if >1 cm versus 55% if <1 cm). Overall, its diagnostic accuracy is similar to TEE for vegetation and new PV dehiscence, but remains lower for leaflet perforation.[6,7] On the other hand, the ability of multidetector CT 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.[8]

The shortcomings of the diagnosis of DIE based on morphological changes have triggered an increasing use of SPECT

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circulation*. 2015;132:1076-1080.
DOI: 10.1161/CIRCULATIONAHA.115.018521.)

***Circulation* is available at http://circ.ahajournals.org**
DOI: 10.1161/CIRCULATIONAHA.115.018521

and PET for the evaluation of the increased metabolic activity caused by the infection before 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 radiolabeled leukocytes and ^{18}F-FDG PET/CT in the diagnosis of DIE in patients with a negative or inconclusive routine workup with transthoracic echocardiography and TEE[9–19] (Table). Radiolabeled leukocyte SPECT/CT imaging seems to be more specific for the detection of infective endocarditis and infectious foci than ^{18}F-FDG PET/CT. However, ^{18}F-FDG PET/CT is likely the preferred imaging technique, because SPECT/CT is less sensitive, more time consuming, and requires leukocyte labeling.[1,16] ^{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[15] showed that adding abnormal FDG uptake around a PV to the modified Duke criteria at admission increased the sensitivity for the diagnosis of PV endocarditis from 70% to 97%. This result was attributable to a significant reduction in the number of possible PV endocarditis 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 postimplantation phenomena (eg, pocket hematoma, inflammation).[9–14] Interestingly, several reports showed that FDG-PET/CT could detect clinically unsuspected sites of extracardiac infection in up to 10% to 28% of cases.[18,19]

In this issue of *Circulation*, Pizzi et al[17] evaluated the incremental value of ^{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). 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 infective endocarditis 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 periannular 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 PV endocarditis, but not in intracardiac devices, maybe because of 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 nonconclusive echocardiography when adopting accurate patient selection and inclusion criteria by an expert endocarditis team.[9–16] The benefits of PET/CT(A) are mostly related to the early identification of endocardial involvements, better evaluation of perivalvular lesions, and documentation of extracardiac complications (silent embolic events or metastatic infectious events) or associated features (ie, neoplastic lesions; Figure). Abnormal FDG (or radiolabeled leukocyte SPECT) uptake around PV and definite perivalvular lesions on cardiac CT are considered major Duke criteria in the 2015 European Society of Cardiology guidelines, whereas an embolic event detected by imaging only represents a minor criterion.[1] A class IIb recommendation have been made for intracardiac devices.[1] 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.[17] Additional potential roles of PET/CT in DIE, although 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 (eg, 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

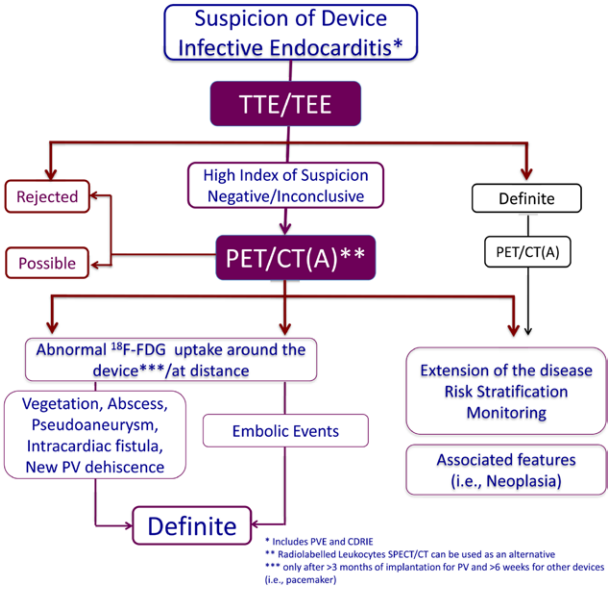

Figure. Potential roles of PET/CT(A) in device infective endocarditis. CTA indicates computed tomography angiography; and PET, positron emission tomography.

Table. Role of ^{18}F-FDG PET/CT in Suspected Device Infective Endocarditis

Authors (Years and Reference)	Population	Method	Site of Infective Endocarditis
Bensimhon et al (2011)[9]	n=21 with suspected CIED infection + 14 controls	• ^{18}F-FDG PET/CT • 15 under antibiotic treatment	• Pacemaker • Implantable defibrillator
Sarrazin et al (2012)[10]	n=42 with suspected CIED infection + 12 controls	• ^{18}F-FDG PET/CT	• Pacemaker
Cautela et al (2013)[11]	n=21 with CIED infection (13 with CDRIE)	• ^{18}F-FDG PET/CT • 11 under antibiotic treatment	• Pacemaker • Implantable defibrillator
Leccisotti et al (2014)[12]	n=27 with suspected CIED infection +15 controls	• ^{18}F-FDG PET/CT • Standard protocol (1H) • Delayed protocol (3H) • All under antibiotic treatment	• Pacemaker • Implantable defibrillator
Graziosi et al (2014)[13]	n=27 with suspected CIED infection	• ^{18}F-FDG PET/CT	• Pacemaker • Implantable defibrillator
Ahmed et al (2015)[14]	n=46 with suspected CIED infection + 40 controls	• ^{18}F-FDG PET/CT • 6 wk postimplantation	• Pacemaker • Implantable defibrillator • Resynchronizer
Saby et al (2013)[15]	n=72 with suspected PVE	• ^{18}F-FDG PET/CT • Median time 9 days • 55 under antibiotic treatment	• 44 biological PV • 28 mechanical PV
Rouzet et al (2014)[16]	n=39 with suspected PVE	• ^{18}F-FDG PET/CT • Radiolabeled leukocyte SPECT/CT • 28 under antibiotic treatment	• 24 biological PV • 13 mechanical PV • 2 others
Pizzi et al (2015)[17]	n=92 with suspected DIE	• ^{18}F-FDG PET/CT(A) • CTA in 76 cases • Median time 7 days • All under antibiotic treatment	• 40 biological PV • 25 mechanical PV • 25 pacemaker • 11 implantable defibrillator/ resynchronizer • 10 others

Table continued on the following page.

CDRIE indicates cardiac device–related infective endocarditis; CIED, cardiac implantable electronic device; CT, computed tomography; CTA, CT angiography; DIE, device infective endocarditis; FDG, fluorodeoxyglucose; IE, infective endocarditis; PET, positron emission tomography; PV, prosthetic valve; PVE, prosthetic valve endocarditis; SPECT, single-photon emission computed tomography; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography

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 (postoperative inflammatory response with possible false-positive responses) or the initiation of antimicrobial treatment (risk of false-negative cases) remains unknown. Last, whether PET/CT(A) would contribute to shorten the hospital stay, prevent clinical complications, and reduce the cost of hospitalization also needs to be elucidated.

Disclosures

None.

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Exclusion Criteria	Final Diagnosis	Duke Criteria	^{18}F-FDG PET Results	Duke Criteria + ^{18}F-FDG PET/CT
• Not specified	• Definite IE=10	• Not specified • Positive TEE (performed in 16 cases) for vegetation in 31%	Generator • Sensitivity=80% • Specificity=100% Leads • Sensitivity=60% • Specificity=100%	• Not specified
• Not specified	• Definite IE=35	• Not specified • Positive TEE 54.5%	• Sensitivity=88.6% • Specificity=85.7%	• Not specified
• Not specified	• Definite IE=7 • Possible IE=6	• Not specified • Positive TTE/TEE in 77%	• Sensitivity=30.8% • Specificity=62.5%	• Not specified
• Pregnancy • Hemodynamic instability • Inability to lie flat • Diabetes mellitus	• Not specified	• Not specified • Positive TEE for vegetation in 52%	Standard • Sensitivity=86% • Specificity=100% Delayed • Sensitivity=91% • Specificity=100%	• Not specified
• Not specified	• Definite IE=5 • Possible IE=10 • Rejected IE=12	• Negative echo in 56% but TEE performed only in 27% of cases	• Sensitivity=63% • Specificity=86%	• Reclassification of 48% of cases
• Not specified	• Definite PVE=20 • Possible PVE=26	• Not specified	• Sensitivity=97% • Specificity=98%	• Not specified
• Pregnancy • Inability to lie flat • Need for urgent cardiac surgery • Hemodynamic instability • Cardiac surgery<1 mo • Blood glucose level >1.8 g/L	• Definite PVE=30 • Possible PVE=22 • Rejected PVE=20	• Sensitivity=70% • Specificity=80%	• Sensitivity=73% • Specificity=80%	• Sensitivity=97% • Specificity=40% • Net reclassification index=10.3%
• Stimulation device • Vascular prosthesis • Left ventricular assist device • Complicated PVE requiring immediate surgery	• Definite PVE=14 • Possible PVE=4 • Rejected PVE=21	• Not specified	• Sensitivity=93% • Specificity=71%	• Reclassification of 46% of cases
• Need for urgent cardiac surgery • Hemodynamic instability	• Definite PVE=52 • Possible PVE=5 • Rejected PVE=35	• Sensitivity=51.3% • Specificity=92% • Similar for PVE and DIE	• Sensitivity=87.2% • Specificity=92% • Similar for PVE and DIE	• Sensitivity=89.7% • Specificity=88% • Reclassification of 90% of possible IE

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KEY WORDS: Editorials ■ cardiac imaging techniques ■ echocardiography