

¹⁸F-FDG PET/CT in the Diagnostic Workup of Infective Endocarditis and Related Intracardiac Prosthetic Material: A Clear Message

Anna Gomes¹, Riemer H.J.A. Slart^{2,3}, Bhanu Sinha¹, and Andor W.J.M. Glaudemans²

¹Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands;

²Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; and ³University of Twente, Biomedical Photonic Imaging Group, Enschede, The Netherlands

Infective endocarditis (IE) is a devastating disease with high fatality rates. Its incidence is increasing because the number of procedures in which prosthetic material is implanted in the heart is growing. Reported overall in-hospital mortality is 20%, and 1-y mortality is 40% with aggressive treatment (1). This detrimental infectious disease is mainly caused by bacteria (most being gram-positive bacteria, of which 80% are staphylococci, streptococci, and enterococci), but also fungi have been reported as causal microorganisms. The pathophysiology of IE involves local spread of infection, metastatic infection, embolic foci, and immune-mediated damage, causing a variety of symptoms and signs. Acutely life-threatening complications are major cerebral or coronary embolization from vegetations, chordal rupture, and valve perforation. In clinical practice, the modified Duke criteria (a constellation of major and minor clinical, microbiologic, and anatomic criteria) have been used as guidance for diagnosing patients

Complicating factors in this patient group are uncertainties about the pathophysiology and thereby definition of infection. ICEDs consist of intracardiac and extracardiac leads and an extracardiac generator. Infection can be located at the generator pocket and the leads but also can cause ICED-related IE. Generator pocket infection, lead infection, and ICED-related IE frequently coexist (2), and some people even state that leads are always infected with generator pocket infection because of biofilm formation. Because both antimicrobial treatment and surgical management largely depend on these definitions, they are highly relevant. Standard management in ICED-related lead infection or IE is full removal of the device. Furthermore, the modified Duke criteria have never been validated for ICED-related infection but may be used to guide diagnosis in this condition (2). Sensitivity of the modified Duke criteria can be further increased by adding evidence of pocket infection and echocardiographic evidence of lead vegetations as major criteria. Ten percent of patients undergoing transesophageal echocardiography for reasons other than suspected infection have been reported to show lead masses as an accidental finding. For diagnosis, it is also relevant that clinical or radiologic evidence of pulmonary involvement occurs in 38%–44% of ICED-related IE or lead infection (2).

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suspected of having IE. However, because of the variable clinical presentation of IE in severity as well as further tissue and organ involvement, fast and accurate diagnosis is challenging. This holds true especially in patients with intracardiac prosthetic material in situ, because of acoustic shadowing during echocardiography. Early and correct diagnosis is crucial because consequences in terms of morbidity, mortality, and financial burden in IE and alternative diagnoses are high. A correct diagnosis determines the ability to implement appropriate treatment early, which in turn improves the clinical outcome of IE. Clearly, we are in absolute clinical need of better tools to improve the diagnosis of IE.

Especially, patients with implantable cardiac electronic devices (ICED, such as implantable cardioverter defibrillators and pacemakers) in situ with suspected infection are difficult to diagnose.

In this issue of *The Journal of Nuclear Medicine*, Granados et al. report a large, prospective study evaluating the diagnostic accuracy of ¹⁸F-FDG PET/CT in the diagnostic workup of patients with clinical suspicion of IE or ICED-related infection (3). They included 80 consecutive patients with suspected native valve endocarditis (NVE, $n = 21$), prosthetic valve endocarditis ($n = 29$), and ICED-related infection ($n = 30$). For the total group, sensitivity, specificity, positive predictive value, and negative predictive values of 82%, 96%, 94%, and 87%, respectively, were reported. In the subgroup of patients with intracardiac prosthetic material, these numbers were 96%, 94%, 93%, and 97%, respectively. This is in line with previous reports (4), expanding its evidence base with the largest cohort so far. ¹⁸F-FDG PET/CT was negative in all 6 cases with a final diagnosis of NVE, corroborating the limited sensitivity in this condition, as previously published (4). In this study, ¹⁸F-FDG PET/CT was able to reclassify 90% of the patients initially classified as possible IE according to the modified Duke criteria (63/70): 18 of 70 changed from possible to definite IE, and 45 of 70 were recategorized from possible to rejected IE. This significant reduction of patients, primarily classified as possible IE, is of invaluable clinical importance because this group of patients is confronting us with diagnostic and therapeutic

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For correspondence or reprints contact: Andor W.J.M. Glaudemans, University of Groningen, University Medical Center Groningen, Department of Nuclear Medicine and Molecular Imaging, Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, The Netherlands.

E-mail: a.w.j.m.glaudemans@umcg.nl

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difficulties in daily practice. In addition, in this study, ^{18}F -FDG PET/CT identified 26% of septic embolisms and 10% of malignant foci, numbers also in accordance with previous reports. We certainly agree with the conclusion of the authors that ^{18}F -FDG PET/CT is a useful diagnostic tool. In our opinion, ^{18}F -FDG PET/CT should be included early in the diagnostic workup of patients with suspected intracardiac prosthetic material-related infection according to the criteria of the British Society for Antimicrobial Chemotherapy (2,5). For suspected NVE (according to the British Society for Antimicrobial Chemotherapy criteria), ^{18}F -FDG PET/CT seems generally not useful for the diagnosis of cardiac foci, but it adds important information about extracardiac infectious foci (septic embolism, metastatic infection, portal of entry) and alternative diagnoses. In the study of Granados et al. (3), an alternative condition was diagnosed or predisposing metastatic foci were identified in 47% of suspected NVE cases: an important reason to implement this imaging technique in patients with suspected NVE.

In addition to the diagnostic consequences, ^{18}F -FDG PET/CT has been previously shown to have important therapeutic consequences in a significant number (35%) of cases, for both IE and its extracardiac complications (6). Therapeutic consequences included adjustments of antibiotic regimens, eradication of the port of entry and metastatic foci, indication for surgery (a high negative predictive value helps to select eligible patients to dismiss surgery), prevention of unnecessary device extraction, and length of follow-up. Outcome consequences would ultimately be prevention of relapse, decreased morbidity by reduction of complications and consequently financial costs, and lower mortality. The addition of ^{18}F -FDG PET/CT also showed to be cost-effective in the diagnostic workup of patients with gram-positive bacteremia with high risk of development of metastatic infection (7). ^{18}F -FDG PET/CT has high potential to improve the outcome of patients with suspected IE and device-related infection, because of its availability, easiness to perform, and provision of whole-body sensitive functional information regarding infection, inflammation, and malignancy.

An important aspect in performing ^{18}F -FDG PET/CT in patients with suspected IE is the preparation of patients. The minimum requirements in patient preparation are at least 6 h of fasting and 24 h of a low-carbohydrate- and fat-allowed diet before the scan. As recently published by Scholtens et al. (8), and now confirmed by Granados et al. (3), heparin injection is beneficial to further suppress the myocardial uptake of ^{18}F -FDG. Shortly after cardiac surgery, myocardial ^{18}F -FDG uptake can be false-positive because of the regeneration process with nonspecific inflammation. Therefore, we recommend not to use ^{18}F -FDG PET/CT to diagnose IE within the first month after surgery, in accordance with the guidelines of the European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging for inflammation and infection (9). According to our experience, and supported by Granados et al. (3), visual interpretation of the image using focal or heterogeneous ^{18}F -FDG uptake as a criterion suffices for diagnosis of IE and ICED-related infection, because high interobserver agreement was achieved (92% agreement; κ , 0.81 [$P < 0.01$]) and semiquantitative analysis did not improve diagnostic accuracy. It remains debatable whether previous antimicrobial therapy obscures the accuracy of ^{18}F -FDG PET/CT in diagnosing IE and ICED-related infection. In the study of Granados et al. (3), antibiotic therapy was started in all patients before the scan. No significant difference was found in length of antibiotic therapy between false-negative and true-positive cases ($P = 0.87$). A subsequent issue is whether ^{18}F -FDG PET/CT can be used for the assessment of antimicrobial treatment

efficacy. Efficacy has indeed been shown in single cases, but additional data are needed to validate the use of this technique for this purpose.

In addition to the modified Duke criteria, and importantly, the recent update of the guideline of the European Society of Cardiology for the diagnostic workup of IE includes additional imaging next to echocardiography to obtain anatomic criteria (10). Major criteria for diagnosing IE now also include "abnormal activity around the site of prosthetic valve implantation detected by ^{18}F -FDG PET/CT or radiolabeled leukocytes SPECT/CT" and "definite paravalvular lesions by cardiac CT," and minor criteria now also include vascular phenomena including those detected by imaging only. However, no additional imaging techniques have been proposed for the diagnosis of ICED-related infection (IE, lead, or pocket infection) so far. The study of Granados et al. (3) importantly adds clinically relevant information to this omission by supporting additional imaging tools in the diagnostic workup of patients suspected of having IE or ICED-related infection. Nevertheless, it should be kept in mind that the modified Duke criteria, and additional imaging tools, are supportive in the clinical reasoning process. A multidisciplinary team (including cardiologists, cardiac surgeons, infectious diseases specialists, microbiologists, imaging specialists, and others) has been formally recommended by the updated European Society of Cardiology guideline (level of evidence B), and will ultimately define the final diagnosis (including clinical follow-up) (10).

We strongly feel that the time has come to propagate a clear message, to implement ^{18}F -FDG PET/CT in the diagnostic workup of patients suspected of having IE or ICED-related infection. This imaging technique should be used, in all suitable patients, as an additional tool. It provides complementary information to both transthoracic and transesophageal echocardiography data locally as well as whole-body information on extracardiac foci and complications.

Optimization of patient preparation and scan acquisition is still an important issue to be solved. Further elucidation is needed whether heparin injection before the scan further suppresses myocardial ^{18}F -FDG uptake in addition to diet and fasting. Furthermore, prospective studies are necessary to provide data on scan acquisition improvement by implementation of electrocardiogram-triggered ^{18}F -FDG scanning. Also, simultaneous electrocardiogram-triggered contrast-enhanced multidetector CT scanning provides the opportunity to improve IE diagnosis, because it has been shown to offer high-resolution anatomic information of the heart, blood vessels, and lungs (4). It mainly adds information to echocardiography about perivalvular extension of infection and therefore should be considered as an addition in patients suspected of having IE (4). More data are needed to estimate the effect of antimicrobial therapy before ^{18}F -FDG PET/CT as well as the usability of this scan for monitoring of therapy. The ultimate goal is to be able to provide clear guidance on when to perform ^{18}F -FDG PET/CT both in the diagnostic workup and in the therapeutic setting of the individual patient (personalized medicine). Whether ^{18}F -FDG PET/CT is beneficial to shorten hospitalization, reducing clinical complications and cost, needs to be evaluated in prospective studies. Finally, another interesting future development is the use of hybrid PET/MR imaging camera devices in eligible patients. This combination could be potentially useful because of its lower radiation exposure, unique MRI characteristics, and ability for repetitive scanning, but metal devices need to be MRI-compatible.

DISCLOSURE

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

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