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$^{18}$F-FDG PET/CT with clinical impact in infective endocarditis

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Summary

Imaging modalities are of invaluable importance for the diagnosis of infective endocarditis. Historically, evidence for infective endocarditis by visualisation of structural intracardiac damage has been provided by echocardiography. Nowadays, technological advances enable visualisation of active infection with $^{18}$F-FDG PET/CT, even before ensuing structural damage. This imaging modality is increasingly validated for infective endocarditis. To illustrate this, we propose a change in paradigm by presenting an instructive case report. We suggest that physicians include this functional visualisation of intracardiac infection by $^{18}$F-FDG PET/CT complementary to the anatomical visualisation by echocardiography in the clinical reasoning process. Even with a lack of structural damage there can be a clear need to undergo cardiac surgery to prevent further deterioration, as effective treatment with antimicrobial treatment alone can be unsuccessful. A multidisciplinary endocarditis team should be implemented in every large hospital, as recommended by the European Society of Cardiology 2015 guideline. The nuclear medicine physician and radiologist should be part of this team, presenting the scan results in weekly team meetings, and informing the clinicians about the appropriate indication and interpretation of their imaging modalities.
Introduction

As the evidence for the added value on clinical impact of fluorine-18 fluorodeoxyglucose (18F-FDG) positron emission tomography with computed tomography (PET/CT) scanning in patients with suspicion of infective endocarditis is increasing (1), we promote a shift in paradigm for the management of these patients. In our opinion, the role of 18F-FDG PET/CT in infective endocarditis is clear and it should therefore be implemented in the diagnostic workup of every patient suspected of infective endocarditis, combined with a diagnostic cardiac CT angiography if indicated (1). We support the recommendation of 18F-FDG PET/CT in infective endocarditis by an illustrative case report.

Imaging in infective endocarditis

For the diagnosis of infective endocarditis, imaging has always played an important role. As definite diagnosis is difficult – both concerning sensitivity and specificity – there has always been much uncertainty, discussion, and falsely diagnosed patients with consequently suboptimal therapy and possible development of (fatal) complications. In order to structure and improve the diagnostic workup of patients suspected of endocarditis, the modified Duke criteria were introduced in 2000 (2). The two most important pillars of this scoring system are: 1) identification of the causative pathogen by microbiological methods, and 2) evidence of endocardial involvement as site of destructive infection. Evidence for endocardial infection by visualisation of structural intracardiac damage has been provided thus far by both transthoracic (TTE) and transoesophageal (TEE) echocardiography. Nowadays, technological advances enable visualisation of active endocardial infection in the inflammatory phase with 18F-FDG PET/CT enabling early diagnosis. Thus also enabling earlier start of adequate therapy and prevention of on-going structural damage. Though the use of 18F-FDG PET/CT has already been validated for infective endocarditis (1), we experience various degrees of uncertainty and ambiguity about the implementation of this imaging modality and the use of its results in clinical practice. This is regrettable, as we believe that 18F-FDG PET/CT is clinically important and complementary to echocardiography, depending on the specific clinical situation of the individual patient. 18F-FDG PET/CT should therefore be strongly positioned in the diagnostic workup of patients with (suspected) infective endocarditis.

Echocardiography

Echocardiography is able to visualise anatomical changes of the heart with resulting changes in motility and flow, which develop after the initial inflammatory phase, in a later course of disease. Since echocardiography visualises and quantifies changes in blood flow dynamics, it is able to identify a valve aneurysm, fistula, perforation, valve prolapse, and valve dehiscence by using colour Doppler. In addition, it informs about the size and mobility of vegetation and thereby embolism risk, and in the same investigation provides information about cardiac chamber function (3). Overall, TEE is superior to TTE in the visualisation of infective endocarditis, especially concerning perivalvular complications such as mycotic aneurysms and abscesses and in prosthetic valve endocarditis. TEE also has a major role in surgery: to determine the location and extent of infection, to guide surgery, to assess the result,
and for early postoperative follow-up (4). However, superiority of either one of these modalities also depends on the location of the infection. TTE generally allows a better view of the right heart (excluding infection at the pulmonary valve and unusual locations such as the Eustachian tube or Chiari network), and of small anterior abscesses of the aortic valve (3,4). Unfortunately, echocardiography fails to detect infectious complications in 30% of patients, especially in those with intracardiac prosthetic material in situ as these patients present with perivalvular complications at a particularly high rate (1). Therefore, alternative imaging modalities, providing complementary information, are needed. \(^{18}\)F-FDG PET/CT may play a pivotal role here for optimal detection of cardiac infection complications in patients with intracardiac prosthetic material as well as extracardiac foci in all patients with infective endocarditis. Echocardiography will continue to be the first line imaging tool, and seems to be especially meaningful in the intracardiac diagnosis of native valve endocarditis, as well as for the visualisation of (especially smaller size) vegetation (1).

**\(^{18}\)F-FDG PET/CT**

\(^{18}\)F-FDG PET/CT provides functional data on the intracardiac extent of infection before structural damage takes place, as well as extracardiac information about metastatic and embolic sites of infection, including the port of entry of the inflicting microorganism. The added diagnostic value of \(^{18}\)F-FDG PET/CT has been demonstrated for intracardiac infections in patients with intracardiac prosthetic material after an appropriate post-surgical interval of 1-3 months (1,4). Important for optimal diagnostic accuracy is to prepare the patient adequately before the acquisition of the scan by fasting for at least 6 hours and a low carbohydrate, fat-allowed diet for at least 24 hours. It is important to identify intracardiac sites of infection early as it might enable treatment of the infection in the inflammatory phase before development of structural damage and further related complications. Perivalvular complications and valve dehiscence require urgent cardiac surgery and therefore prevention of this sudden occurrence is of invaluable importance. Important anatomical information can be provided in this regard by ECG-triggered diagnostic cardiac CT angiography, especially concerning perivalvular extension of infection (abscesses, pseudo-aneurysms, fistulas, and valve dehiscence with paravalvular leakage). If correctly indicated, the additional use of this diagnostic cardiac CT can further increase the impact of the \(^{18}\)F-FDG PET/CT on the therapeutic regimen.

The added diagnostic value of \(^{18}\)F-FDG PET/CT for extracardiac infection concerns all patients with a proven intracardiac infection (both native and prosthesis-related) (1). Extracardiac sites of infection are important to identify as they may require separate active treatment and follow-up to eliminate them as potential persistent sources of pathogen seeding (with possible reinfection of newly implanted prosthetic material).

A drawback of imaging with \(^{18}\)F-FDG PET/CT is the limited specificity for infection, as it is positive for all tissues with avid glucose uptake, such as malignant tumors and inflammation by other causes. Consequently, in order to limit the rate of false-positive results it is important to interpret a scan with sufficient information about the clinical situation of a patient. Scanning with \(^{18}\)F-FDG PET/CT may
produce unwanted knowledge about metabolically active sites in the body that need additional follow-up to assort their nature and might require therapy.

The interpretation of a $^{18}$F-FDG PET/CT scan as either negative or positive for infective endocarditis is based on the intensity, distribution and pattern of $^{18}$F-FDG uptake as diagnostic criteria. To improve the reliability of clinical applicability and interpretation of $^{18}$F-FDG PET/CT, criteria need to be developed that become incorporated into guidelines.

Furthermore, the extent to which this scan has immediate therapeutic consequences depends on the specific clinical situation of the individual patient. Visualisation of infectious complications providing an indication for cardiac surgery are historically critically important in all patients with infective endocarditis: abscess, false aneurysm, fistula, and a large/growing vegetation (4). However, in patients with intracardiac prosthetic material *in situ*, evidence of an infected prosthesis can nowadays be sufficient to trigger surgical intervention, even without the visualisation of further structural damage. Prosthetic valve endocarditis can be adequately treated with antimicrobial therapy alone under specific conditions (5-8). However, presence of infection of implanted prosthetic material is generally an indication for removal of this material, as it is considered a source of ongoing infection that often cannot be controlled with antimicrobial therapy alone (4,5,9). Visualisation of intracardiac structural damage was historically required for the decision to operate, but nowadays visualisation of infected prosthetic material prior to structural damage should be taken into consideration as an indication for early surgical intervention. $^{18}$F-FDG PET/CT should become an important additional tool in the multidisciplinary decision making process on the optimal therapy for an individual patient, taking comorbidity and risks of surgical consequences into account.

**Paradigms**

It involves a change in paradigm to start including the functional visualisation of intracardiac infection by $^{18}$F-FDG PET/CT as complement to the structural visualisation by echocardiography in the therapeutic decision making process. This change in paradigm has been put forward most clearly in the guideline of the European Society of Cardiology (4), and is also mentioned in that of the American Heart Association (9).

We experience that this change in paradigm represents a revolution in daily clinical practice for clinicians taking care of patients with infective endocarditis. Furthermore, we experience uncertainty and ambiguity about the reliability of image interpretation, especially a lack of confidence in the (positive) predictive value. Cardiothoracic surgeons might perceive it as bold to proceed to surgery without visual proof of mechanical reasons to correct cardiac anatomy in the course of this disease. A further, potentially complicating, matter is the perceived threshold by cardiothoracic surgeons in the use of mortality rate of their elective procedures as an indication for their quality. Unfortunately, this obstructs good clinical care if the patients’ individual context and stratification is not taken into consideration. Therefore, in our view, the inclusion of the functional information provided by $^{18}$F-FDG PET/CT in the therapeutic decision making process can be justified in several cases since delayed intervention may often increase severe morbidity and mortality.
We are convinced that the additional use of $^{18}$F-FDG PET/CT for the diagnosis of infective endocarditis is supported by the following arguments: 1) visualisation of structural damage usually occurs late in the disease process; 2) false negative results with echocardiography alone occur in an important percentage of patients; and 3) in the decision to proceed to cardiac surgery or not, the decision is not only about current haemodynamic cardiac function, but also about future opportunities for the patient to undergo surgery. Delay of surgery may decrease the prognosis of the patient or result in the development of physical conditions in which the patient is no longer eligible for cardiac surgery – these may be e.g. cardiac, pulmonary, cerebral, or renal. Furthermore, the development of extracardiac infectious foci may jeopardise the prognosis due to their ability to re-infect the freshly implanted prosthetic material without adequate antimicrobial therapy. Of course, the lack of specificity of the $^{18}$F-FDG PET/CT should also be taken into account in the clinical decision making process, as unnecessary surgery is a burden to the patient and healthcare system.

**Multidisciplinary workup**

Ultimately, the optimal therapeutic regimen should be determined by a multidisciplinary team carefully considering the information provided by the modified Duke criteria and new diagnostic modalities on the one hand and their potential pitfalls on the other hand, always in light of the specific clinical situation for the individual patient. Therefore, starting the formalisation of a multidisciplinary endocarditis meeting and team to discuss the optimal diagnostic workup and therapeutic regimen of individual patients is important, as well as the inclusion of experienced nuclear medicine physicians and radiologists (imagers). The knowledge about false positive and false negative $^{18}$F-FDG PET/CT scans is currently incomplete, but this modality gives us the opportunity for more focused treatment, earlier in the course of disease and for possible prevention of new complications. Nevertheless, we need to increase our knowledge about sources of false results with the use of this imaging modality in clinical practice and future scientific studies need to clarify this topic.

**Case report**

In this illustrative case report, $^{18}$F-FDG PET/CTA was performed in a 57 year old male patient with non-specific symptoms of stiff joints (with previous Reiter’s syndrome), possible Raynaud’s disease and unexplained high inflammatory parameters. His clinical history mentioned a Bentall procedure in two stages. First, his aortic valve was replaced by a mechanical prosthetic valve 7 years ago, because of significant stenosis. Second, replacement of his aortic root and ascending aorta with re-implantation of the coronary arteries was performed 2 years ago, because of an ascending aorta aneurysm. His clinical history also included a transient ischaemic attack 6 months ago. $^{18}$F-FDG PET/CTA with appropriate dietary preparation showed paravalvular uptake of FDG on the left side of the aortic prosthetic valve with a large contrast filled cavity, indicating active infective endocarditis with a paravalvular abscess and some pannus on the left side (see figure). Additionally, increased FDG uptake was shown in enlarged mediastinal lymph nodes and in multiple spleen abscesses. A following TTE did not reveal any vegetation, nor did TEE. However, at the same time-point, TEE did show a paravalvular cavity around the aortic valve communicating with the left ventricular outflow tract, and a mild aortic valve insufficiency.
After taking blood cultures, intravenous vancomycin (1500 mg loading dose, and thereafter 2500 mg/24 hours continuously) and gentamicin (250 mg once daily) were simultaneously started as empirical therapy for prosthetic valve infective endocarditis. Blood cultures remained negative. The patient was deemed eligible for surgery, but only after eradication of his spleen abscesses. Therefore, the patient first underwent splenectomy. Microscopy of pus from the splenic abscesses showed Gram-positive rods, after which gentamicin was replaced by intravenous ceftriaxone (2000 mg once daily). Finally, the patient underwent another Bentall procedure 1 month after the initial visualisation of the aortic prosthetic valve infective endocarditis on $^{18}$F-FDG PET/CT. As molecular testing on the explanted material during cardiac surgery showed *Propionibacterium acnes* as pathogen, the patient was treated with ceftriaxone for another 6 weeks after his surgery. At follow-up 3 months after surgery, and 6 weeks after stopping his antibiotic treatment, this patient showed good clinical recovery from his aggressively treated infective endocarditis, which was initially diagnosed on $^{18}$F-FDG PET/CT.

This successful case illustrates the importance of both the $^{18}$F-FDG PET and CTA scan in the diagnostic workup and therapeutic decision-making process for patients suspected of infective endocarditis. This case also emphasises the importance of $^{18}$F-FDG PET/CT in the identification of extracardiac infectious foci which may complicate a case of infective endocarditis.

[A] Coronary MIP FDG-PET image showing increased FDG uptake at the site of the prosthetic valve (red arrows), at multiple mediastinal and hilar lymph nodes (yellow arrows) and in the spleen (green arrows), suggestive of multiple spleen abscesses. [BC] fused transaxial FDG-PET/CT slices showing the increased uptake at the site of the prosthetic valve. [D] fused transaxial FDG-PET/CT slice showing one of the spleen abscesses. [E] fused coronal FDG-PET/CT slice showing increased uptake at mediastinal and hilar lymph nodes.
Our recommendation
To further stimulate the described change in paradigm and include molecular imaging results in the multidisciplinary decision making process for endocarditis patients, we would like to make some suggestions. First, we must start to rely on molecular imaging tools and interpretation concerning the diagnosis of endocarditis, considering the increased sensitivity for early stages of infective endocarditis on the one hand and the limited specificity for infection on the other hand. There is sufficient evidence for this concept. If an experienced nuclear medicine physician concludes that a PET scan is positive for infective endocarditis based on intensity, distribution and pattern of $^{18}$F-FDG uptake as diagnostic criteria for infection, we should include this result in the multidisciplinary decision making process for the optimisation of the individual therapeutic regimen. This is supported by the ESC 2015 modified criteria for the diagnosis of infective endocarditis (4): major criteria include 1) abnormal activity around the site of prosthetic valve implantation detected by $^{18}$F-FDG PET/CT (if implanted more than 3 months previously) and 2) definite paravalvular lesions by cardiac CT; minor criteria include vascular phenomena that are not detected by clinical examination but are detected by imaging only.

Second, we need to start translating imaging with $^{18}$F-FDG PET/CT into a change in the therapeutic regimen if infective endocarditis is suspected. The antimicrobial regimen should be adapted to treat intravascular infection with biofilm formation, which is formed in the infection process of prosthetic material as well as in native valve endocarditis (10). Biofilm demands special antimicrobial agents as they contain bacteria with an altered phenotype in comparison to their free-floating planktonic form, causing them to be challenging to culture and eradicate (10). A surgical plan needs to be discussed in an early phase of disease with the cardiothoracic surgeon as core member of the multidisciplinary endocarditis team. In this meeting, the consequences of a positive $^{18}$F-FDG PET/CT should be (or become) clear to all team members, as well as the chances of successful treatment with antimicrobial therapy alone.

Conclusion
Infective endocarditis remains a complex disease, though there is no magic bullet, we see room for improving diagnosis. We should make more use of $^{18}$F-FDG PET/CT(A) and integrate positive results in the diagnosis of infective endocarditis, based on the currently available evidence and the growing experience of imaging specialists in clinical practice. Even without visualisation of anatomical damage, the need to undergo (early) cardiac surgery should be considered as effective treatment to prevent further deterioration, as opposed to antimicrobial treatment alone. Current challenges with the use of $^{18}$F-FDG PET/CT(A) that remain to be resolved include the lack of standardised criteria for interpretation, sources of false positive and negative results, and discussions about the post-surgical interval in which imaging can be reliably performed. Imaging specialists should promote the value of $^{18}$F-FDG PET/CT for the visualisation of infective endocarditis and provide clear criteria for scan interpretation with a translation in clear results. This will help to convince clinicians that $^{18}$F-FDG PET/CT deserves a prominent position in the workup of suspected endocarditis to prevent serious complications.
References

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