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ORIGINAL PAPER

Diagnostic challenges in infective endocarditis: is PET/CT the solution?

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Abstract

Purpose Despite developments in both imaging and microbiological techniques, the final diagnosis of IE often remains challenging. In this single-center cohort study, we aimed to identify the specific indications for request of ^{18}F-FDG-PET/CT in clinical practice and to evaluate the diagnostic benefit of this nuclear imaging technique.

Methods A total of 235 patients with possible ($n=43$) or definite ($n=192$) IE according to the revised Duke criteria were prospectively studied from July 2013 until December 2016. Echocardiography was generally used as the primary cardiac imaging technique. All patients were treated by a multidisciplinary Endocarditis Team. Diagnostics with ^{18}F-FDG-PET/CT were undertaken on request by at least one member of the multidisciplinary team when overall diagnostics were inconclusive.

Results In 20 patients, ^{18}F-FDG-PET/CT scan was performed for additional diagnostic evaluation. Hereof, 15 patients had a history of implanted cardiac prosthetic material. In six patients with definite IE, the use of ^{18}F-FDG-PET/CT was helpful for further clarification of the diagnosis. In one patient with possible IE, the diagnosis could be reclassified to definite IE. In addition, one case of vertebral osteomyelitis as well as upper and lower leg abscesses and knee empyema were detectable as extracardiac foci. Furthermore, ^{18}F-FDG-PET/CT leads to a modification of the management in five patients.

Conclusion Our findings support the utility of ^{18}F-FDG-PET/CT as an adjunctive diagnostic tool especially in the evaluation of prosthetic valve-/cardiac device-related IE and for the detection of extracardiac foci in some cases. However, due to remaining limitations also of this imaging technique, a multidisciplinary clinical evaluation still remains the essential basis for the diagnostic assessment.

Keywords Infective endocarditis · ^{18}F-FDG-PET/CT · Bioprosthetic valve · Mechanical valve · Intracardiac devices · Multidisciplinary Endocarditis Team

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Introduction

Infective endocarditis (IE) including native valve endocarditis (NVE) as well as intracardiac prosthetic material-related IE is a serious condition affecting about 3–10 per 100,000 persons per year [1, 2]. Despite major advances in diagnostic and therapeutic procedures, the prognosis is poor with a 1-year mortality approaching 30% and high complication rates at long term [3]. Thus, there is a need for improved early diagnosis and optimal management of IE which still remains challenging in daily clinical practice.

Recent guidelines recommend a multidisciplinary Endocarditis Team comprising cardiologists, infectious disease specialists, microbiologists, cardiac surgeons, radiologists, and nuclear medicine physicians to cope with the complexity of the disease [4]. The current standard of assessment is

the revised Duke criteria. These criteria comprise the detection of the causative pathogen and the characterization of endocardial involvement by means of echocardiography as the most important factors for the diagnosis of IE [5]. However, echocardiographic findings often remain ambiguous particularly in the early phase of the disease. In addition, diagnosis is often difficult when foreign material such as cardiac implantable electronic devices or prosthetic valves is present. Whereas echocardiography in general has a specificity > 90%, the sensitivity of transthoracic echocardiography (TTE) for the diagnosis of vegetations ranges from 20 to 65% and can be improved to up to 90% using transesophageal echocardiography (TEE) [6]. Although the overall level of diagnostic performance is high, there are a number of pitfalls in the analysis of vegetations leading to false positive or negative findings. As a result, other imaging techniques such as positron emission tomography (PET) with the glucose analogue [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) have recently been proposed in guidelines to improve diagnostic accuracy in cases of suspected IE and diagnostic difficulties [4]. Recent data have underlined the usefulness of ^{18}F-FDG-PET/CT in diagnosing and monitoring infectious conditions [7]. However, even this methodology exhibits several limitations and randomized controlled trials are lacking.

The goal of our endocarditis cohort study was to identify the specific indications to perform ^{18}F-FDG-PET/CT and to evaluate the diagnostic relevance of this technique.

Materials and methods

Patients

This is a retrospective analysis of prospectively collected data. In our single-center cohort study, all patients were included that were standardly evaluated by a multidisciplinary Endocarditis Team at the University Hospital of Cologne, Germany between July 2013 and December 2016 for definite or possible native valve (NV), prosthetic valve (PV), or cardiac implantable electronic device (CIED)-related endocarditis according to the revised Duke criteria [5].

Clinical history and findings from detailed physical examination as well as results of echocardiography, blood cultures, and serum markers of inflammation (leukocytes, C-reactive protein, and erythrocytes sedimentation rate) were collected.

TTE was used as the primary cardiac imaging technique in all patients. Additional TEE was performed when (a) initial TTE was positive, (b) there was high clinical suspicion of endocarditis despite negative TTE, (c) a poor quality of TTE, or (d) a suspected prosthetic valve endocarditis and/or intracardiac devices. TEE was standardized and interpreted by an experienced cardiologist. It was performed in all except one patient who had esophageal stenosis.

All patients received a bedside consultation of an experienced infectious disease consultant and were entered in the Endocarditis Registry of the University Hospital of Cologne in case of possible or definite infective endocarditis according to the revised Duke criteria, which were applied as the gold standard in our study. Further imaging with ^{18}F-FDG-PET/CT was undertaken when requested by at least one member of the multidisciplinary team for diagnostic clarification. When more than one ^{18}F-FDG-PET/CT or TEE per patient was performed, only the first diagnostic imaging result was used for further evaluation in this study.

The study was approved by the Ethics Committee of the medical faculty at the University Hospital of Cologne (vote 14–221). Since diagnosis and treatment correspond to the quality standard of current guidelines, no written informed consent of the patients was considered necessary. However, patients were asked for written informed consent to the ^{18}F-FDG-PET/CT examination. This study was registered at the U.S. National Library of Medicine [NCT02388893, Endocarditis Registry of the University Hospital of Cologne (ER-UHC)].

^{18}F-FDG-PET/CT

^{18}F-FDG-PET and combined low-dose CT scans were obtained using a Siemens Biograph until end of 2014 and since then a Siemens Biograph mCT Flow 128 Edge (Siemens Medical Solutions, Erlangen, Germany). All patients were asked to fast for an extended period of at least 12 h before scanning. During the study period, a diet with a meal rich in fat and low in carbohydrates in the days prior to the exam was not yet routinely implemented and also heparin was not part of the routine protocol. Blood glucose levels were checked before ^{18}F-FDG injection. Approximately 60 min after injection of 350 MBq^{18}F-FDG, image acquisition in 3D-mode was commenced. All emission data were corrected for attenuation, randoms, scatter, and decay. Attenuation correction was performed using an unenhanced low-dose CT scan (120 kV, mA modulation, pitch 1.2, and slice thickness 5.0 mm). Reconstruction was conducted with an ordered subset expectation maximization (OSEM) algorithm with 4 iterations and 12 subsets and Gauss-filtered to a transaxial resolution of 5 mm at full-width at half-maximum (FWHM). Images were viewed on a Siemens workstation, permitting simultaneous viewing in all three planes with easy cross-referencing between planes.

All cases were reviewed by an experienced nuclear medicine physician. Visual analysis determined whether the examination was positive when focal areas of increased uptake of ^{18}F-FDG in the valve area were seen and the uptake was confirmed on non-attenuation corrected images.

Results

A total of 235 patients with possible ($n=43$) or definite ($n=192$) IE were prospectively registered during the study period. In 29 cases, ^{18}F-FDG-PET/CT was performed as an additional diagnostic imaging method, and 20 patients were eligible for further evaluation within this study (see Fig. 1).

Patient characteristics are summarized in Table 1. Of the 20 included patients, 12 individuals were classified as definite and eight as possible IE according to the revised Duke criteria. 15 out of 20 patients had a history of valve or aortic replacement/reconstruction or implantation of intracardiac devices.

Table 2 gives a detailed overview of the major and minor criteria according to the revised Duke criteria together with the indications and results for the ^{18}F-FDG-PET/CT images. Indications for additional nuclear medicine imaging were diagnostic uncertainty due to artificial heart valves ($n=9$), followed by overall inconclusive clinical assessment ($n=5$) and search for other foci than cardiac ($n=3$) or a combination of these factors ($n=3$). Eventually, one single case of vertebral osteomyelitis, knee empyema as well as upper and lower leg abscesses were detectable as other foci than cardiac. In the subgroup of patients with definite IE, ^{18}F-FDG-PET/CT was considered helpful as an additional tool especially due to diagnostic uncertainties in TEE ($n=5$, artificial heart valve; $n=1$, assist device; $n=2$, degenerative heart valve) and the suspicion of other infectious foci ($n=2$) or inconclusive clinical assessment ($n=2$). With regard to the latter, one patient suffered from recurrent bacteremia without any signs of IE in repeated TEE and had a history of periprothetic hip infection. The second patient suffered from recurrent bacteremia and back pain. On this background, uncertainties remained regarding discreet abnormalities in TEE.

^{18}F-FDG-PET/CT images showed cardiac uptake in only 6 out of 12 patients classified as definite IE and in one out of 8 patients classified as possible IE. Thus, PET/CT scan was confirming concerns of the multidisciplinary Endocarditis Team in 35% (7/20) of all cases. Figure 2 shows the overlap of positive PET/CT images with fulfilled major criteria of echocardiography and microbiology. The positive PET/CT results ($n=7$) were exclusively observed when blood culture results fulfilled major criteria according to the revised Duke criteria either with ($n=5$) or without ($n=2$) positive echocardiographic findings. In four cases, other infectious foci could be detected with either positive ($n=1$) or negative ($n=3$) ^{18}F-FDG-PET/CT results regarding IE. In the other 13 patients, nuclear imaging was not helpful for further clarification of the IE diagnosis.

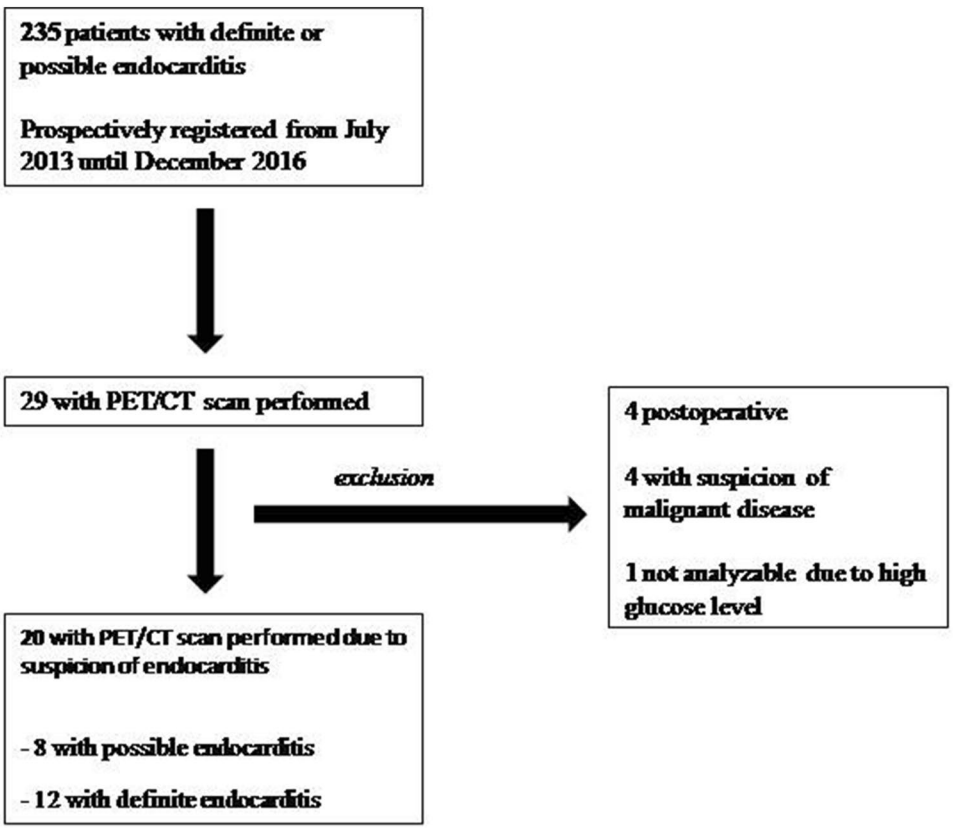

Fig. 1 Diagram of patient selection

Table 1 Baseline characteristics of the study population

General information	
Number of patients (*n*)	20
Age [median, (IQR)]	72 (64–79)
Sex [male (%)]	14 (70)
Endocarditis according to revised Duke criteria (*n*)	
Definite	12
Possible	8
Microbiological etiology—major criteria	
Staphylococcus aureus	5
Enterococcus faecalis	5
Streptococcus spp.	3
Staphylococcus epidermidis	1
Escherichia coli	1
Microbiological etiology—minor criteria	
Enterococcus faecalis	1
Staphylococcus haemolyticus	1
Klebsiella pneumoniae	1
Valve/aortic replacement or reconstruction/intracardiac devices	
N	15
BPV (*n*)	7 [AV (4) + PM (1); AV + MIV (1); AV + aortic root reconstruction (1); Mitral valve reconstruction (1)]
MV (*n*)	4 [AV (2) + ICD (1); AV + MIV (1); AV and aorta ascendens reconstruction (1)]
ICD (*n*)	2
PM (*n*)	1
Ventricular assist device (*n*)	1
Time from implantation to PET—months [median, (IQR)]	
All	26 (3–48)
Valves/reconstructions only	21 (2–72)
Intracardiac devices only	42 (23–64)
Time from blood culture positivity to diagnostic imaging—days [median, (IQR)]	
Transesophageal echocardiography	3 (2–6)
^{18}F-FDG-PET/CT	12 (8–18)
Laboratory values at time of PET [median, (IQR)]	
CRP (mg/dl), normal range < 5 mg/dl	26 (8–57)
Leucocytes (/µl), normal range 4000–10,000/µl	6 (5–11)
ESR (mm/h), normal range < 5 mm/h ($n = 18$)	56 (23–79)

AV aortic valve, *BPV* bioprosthetic valves, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ICD* implantable cardioverter defibrillator, *IQR* interquartile range, *MV* mechanical valves, *MIV* mitral valve, *PM* pacemaker

More importantly, in 5 out of 20 cases (25%), ^{18}F-FDG-PET/CT results helped us to modify the management of patients by confirmation of IE diagnosis ($n = 1$), identification of knee empyema ($n = 1$), rejection of IE ($n = 1$), confirmation of IE diagnosis with identification of vertebral osteomyelitis ($n = 1$) and by diagnosing a drive-line associated infection ($n = 1$). This led to a prolongation of antibiotic therapy in three patients, shortening in one patient and surgical intervention in two patients.

Discussion

In this endocarditis cohort study, in only a minority of 20 out of 235 patients, ^{18}F-FDG-PET/CT was performed. With help of ^{18}F-FDG-PET/CT, one patient with possible IE diagnosis could be reclassified to definite IE, and in six patients with definite IE, the diagnosis could be confirmed against the background of the previous diagnostic

Table 2 Revised major and minor criteria according to Duke and ^{18}F-FDG-PET/CT indications/results of the study population

Patient	Major criteria		Minor criteria						PET indication	PET result of endocard
	Echo-cardiography	Blood culture	Blood culture	Predisposition	Fever	Vascular signs	Immunologic signs	Other Foci		
Patients with definite endocarditis										
1	Positive	Positive (*S. aureus*)	n.a.	Yes (BPV)	Yes	No	No	No	Diagnostic insecurity due to artificial heart valve	Positive
2	Positive	Positive (*E. faecalis*)	n.a.	Yes (MV)	Yes	Yes (Cerebral embolisms)	No	No	Diagnostic insecurity due to artificial heart valve	Positive
3	Positive	Positive (*E. coli*)	n.a.	Yes (BPV)	Yes	No	No	No	Diagnostic insecurity due to artificial heart valve	Positive
4	Positive	n.a.	Positive (*K. pneumoniae*)	Yes (BPV)	Yes	No	No	No	Diagnostic insecurity due to artificial heart valve, pathogen not typical	Negative
5	Positive	Positive (*S. aureus*)	n.a.	No	Yes	No	No	Abscess right lower leg (PET-positive)	Other infectious foci	Negative
6	Positive	Positive (*S. aureus*)	n.a.	Yes (MV, ICD)	Yes	No	No	No	Diagnostic insecurity due to artificial heart valve	Positive
7	Positive	Positive (*S. epidermidis*)	n.a.	No	No	No	No	Knee joint empyema (PET-positive)	Diagnostic insecurity due to degenerative valve alterations	Positive
8	Negative	Positive (*E. faecalis*)	n.a.	Yes	Yes	Yes (cerebral embolisms)	No	No	Diagnostic insecurity due to degenerative valve alterations	Positive
9	Positive	Positive (*S. aureus*)	n.a.	No	Yes	No	No	No	Clinical assessment not conclusive	Negative
10	Negative	Positive (*E. faecalis*)	n.a.	Yes (BPV, PM)	Yes	Yes (splenic embolisms)	No	No	Clinical assessment not conclusive	Negative

Table 2 (continued)

Patient	Major criteria		Minor criteria						PET indication	PET result of endocard
	Echo-cardiography	Blood culture	Blood culture	Predisposition	Fever	Vascular signs	Immunologic signs	Other Foci		
11	Positive	Positive (*S. oralis*)	n.a.	Yes (assist device)	Yes	No	No	No	Diagnostic insecurity due to Assist device	Negative
12	Positive	Positive (*S. aureus*)	n.a.	No	Yes	Yes (Janeway lesions)	No	Femur abscess (PET-positive)	Other infectious foci	Negative
Patients with possible endocarditis										
13	Negative	n.a.	Positive (*E. faecalis*, only once pos.)	Yes (BPV)	No	No	No	No	Diagnostic insecurity due to artificial heart valve	Negative
14	Positive	n.a.	Positive (*S. haemolyticus*)	Yes (mitral valve reconstruction)	No	No	No	No	Diagnostic insecurity due to artificial heart valve	Negative
15	Positive	Negative	Negative	Yes (ICD)	Yes	No	No	No	Clinical assessment not conclusive	Negative
16	Negative	Positive (*E. faecalis*)	n.a.	Yes (BPV)	Yes	No	No	Vertebral osteomyelitis (PET-positive)	Other infectious foci	Positive
17	Negative	Positive (*S. gallolyticus*)	n.a.	Yes (MV, aorta ascendens reconstruction)	Yes	No	No	No	Clinical assessment not conclusive	Negative
18	Negative	Positive (*S. species*)	n.a	yes (MV)	Yes	No	No	No	Diagnostic insecurity due to artificial heart valve	Negative
19	Negative	Positive (*E. faecalis*)	n.a.	Yes (PM)	Yes	No	No	No	Diagnostic insecurity due to pacemaker	Negative
20	Positive	Negative	Negative	Yes (ICD)	Yes	No	No	No	Clinical assessment not conclusive	Negative

BPV bioprosthetic valve, *E. coli Escherichia coli, E. faecalis Enterococcus faecalis*, ICD implantable cardioverter defibrillator, *K. pneumoniae Klebsiella pneumoniae, MV* mechanical valve, *N.a.* not applicable, *PM* pacemaker, *S. aureus Staphylococcus aureus, S. epidermidis Staphylococcus epidermidis, S. haemolyticus Staphylococcus haemolyticus, S. gallolyticus Streptococcus gallolyticus, S. oralis Streptococcus oralis, S. species Streptococcus species*

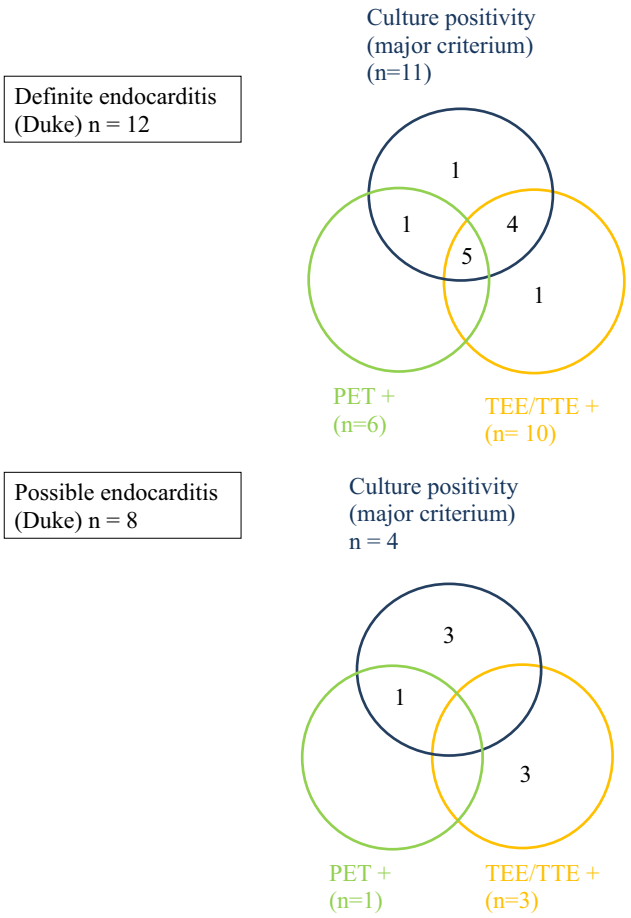

Fig. 2 Diagnostic overlap in definite and possible endocarditis according to the revised Duke criteria

uncertainties. Furthermore, ^{18}F-FDG-PET/CT led to a modification in the management of five patients.

In recent years, the use of ^{18}F-FDG-PET/CT has proven helpful in diagnosing inflammatory and infectious diseases and a few reports have even shown promising results in the field of IE [8]. Both the American Heart Association and the European Society of Cardiology propose the usefulness of ^{18}F-FDG-PET/CT to reduce the number of misdiagnosed IE classified in the possible IE category of the revised Duke criteria and to visualize peripheral embolic events [4, 9]. However, to the present day, there is no specific or formal recommendation in the current guidelines for routine use in daily clinical practice. Especially, the AHA statement emphasizes that more studies are needed to determine the role of ^{18}F-FDG-PET/CT in the management of patients with IE [9]. In our cohort, particularly, when positive results in TEE or of blood cultures were reported, but overall diagnosis was inconclusive, ^{18}F-FDG-PET/CT contributed to the clarification of the diagnosis of IE and had the potential to detect extracardiac manifestations of the disease.

The high number of patients (12/20) who were additionally tested with ^{18}F-FDG-PET/CT despite definite IE according to the revised Duke criteria reflects the challenge to diagnose IE [10]. One of the causative factors is that the aforementioned criteria have a sensitivity of approximately 80% when they are evaluated at the end of patient follow-up in epidemiological studies, but show a notably lower diagnostic accuracy for early diagnosis in clinical practice [4, 11, 12]. Therefore, it is reasonable to involve a multidisciplinary team including mainly cardiologists, cardiac surgeons, infectious disease specialists, nuclear scientists, and microbiologists in the management of IE which is already recommended by recent guidelines [4, 13]. In a recent observational study with 196 patients, the involvement of an interdisciplinary team led to earlier initiation of specific antibiotic therapy and was an independent predictor of 1-year survival in patients without surgery (HR 0.24, 95% CI 0.07–0.87; $p = 0.03$) [14]. In our cohort, the interdisciplinary decision to perform ^{18}F-FDG-PET/CT leads to an improvement in the management of five patients (25%).

Moreover, recent guidelines emphasize the significance of ^{18}F-FDG-PET/CT in the setting of IE related to foreign material [4]. Previous studies have notably shown the incremental diagnostic value of this nuclear imaging technique in IE especially in case of PVE and devices. For instance, an abnormal FDG uptake around a prosthetic valve as an additional criterion apart from the revised Duke criteria increased the diagnostic sensitivity from 70 to 97%, reducing the number of patients with possible IE from 56 to 32% [15]. In our cohort, 15 out of 20 patients (75%) had prosthetic valve or device-related IE and additional nuclear imaging was particularly beneficial in these patients, since one of our main indications was diagnostic insecurity due to artificial heart valves. Additional indications comprised the detection of extracardiac sites of infection, which is in line with aforementioned studies and guidelines [4, 8, 9]. Thus, in our relatively small cohort, with ^{18}F-FDG-PET/CT, we detected further extracardiac infectious foci in three patients.

However, there are also a number of limitations to ^{18}F-FDG-PET/CT. It is difficult to detect small vegetations (< 5 mm) below the spatial resolution of the PET/CT system. Thus, small vegetations and the inability to correct for cardiac and respiratory motion during routine acquisition as well as a high glucose level especially in diabetic patients may lead to false negative results. False positive results may occur shortly after cardiac surgery or rarely because of concomitant diseases such as primary and secondary tumors of the heart. Moreover, with regard to prosthetic valves or devices, non-specific perivalvular uptake was described years after valve replacement in the absence of infection. Intracardiac leads can be a reason for artifacts, requiring specific corrections during diagnostics [16]. In addition, “false negative” findings have been reported after

prior administration of antimicrobial therapy, rather demonstrating the ability of FDG-PET/CT to monitor a desired response [17]. In recent years, various strategies such as prolonged fasting and unfractionated heparin intravenous administration have been proposed to suppress the physiological uptake of ^{18}F-FDG throughout the heart to improve accurate diagnosis of inflammatory cardiac diseases [18–20]. The rationale behind these strategies is to increase plasma free fatty acid level, which result in a suppression of glucose metabolism that facilitates the detection of areas of myocardial inflammation. In our study, diet with a meal rich in fat and low in carbohydrates in the days prior to the examination was not yet routinely implemented and also heparin was not part of the routine protocol. However, we did not overserve physiological uptake of ^{18}F-FDG in a manner that might have hampered the differentiation of pathological nuclide uptake in the heart.

Conclusion

The final diagnosis of IE often remains difficult. Especially, the growing number of patients with implanted prosthetic material is posing an ever-greater challenge in the future. Particularly, in patients with suspected PVE, the use of ^{18}F-FDG-PET/CT has recently proven to increase diagnostic sensitivity. Our findings support the utility of this nuclear imaging technique as an adjunctive diagnostic tool especially in the evaluation of prosthetic valve-/cardiac device-related IE and for the detection of extracardiac foci. However, due to the remaining limitations of both TTE/TEE and ^{18}F-FDG-PET/CT, the interdisciplinary clinical evaluation still represents the essential basis for the diagnostic assessment.

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Compliance with ethical standards

Conflict of interest C.H. reports personal fees from MSD Sharp & Dohme and Pfizer, lecture fees from Actelion and travel grants from Actelion, Bayer, Orion Pharma and MSD Sharp & Dohme. G.M. received lecture fees from Pfizer, Novartis, Servier, ZOLL, Getinge and Orion Pharma. In the past 3 years, N. Jazmati has received payment for lectures from MSD Sharp & Dohme. C.L. has received honoraria for lectures or travel grants from Abbott, ViiV, Gilead, MSD, and Janssen. In the past 2 years, G.F. has received lecture fees from Bristol Myers Squibb, Janssen Cilag, Merck Sharp & Dohme and Pfizer, travel grants from Gilead and Janssen Cilag, research grants from Gilead, Janssen Cilag, Merck Sharp & Dohme and Roche. G.F. served on advisory boards of Janssen Cilag, Merck Sharp & Dohme, Merck Serono, Pfizer, Roche and Shionogi. In the last 3 years, N. Jung has received lecture fees from Labor Stein, Novartis, Gilead, Infectopharm and MSD and travel grants from Gilead, Novartis and Basilea.

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