

The value of FDG-PET/CT in the diagnostic work-up of extra cardiac infectious manifestations in infectious endocarditis

C. Özcan · A. Asmar · S. Gill · A. Thomassen ·
A. C. P. Diederichsen

Received: 16 January 2013 / Accepted: 15 May 2013 / Published online: 22 May 2013
© Springer Science+Business Media Dordrecht 2013

Abstract Infectious endocarditis (IE) is a serious condition with a high morbidity and mortality. The optimal management of IE depends not only on correct antibiotic therapy and surgery when needed, but involves identification of the portal of entry and detection of extracardiac infectious manifestations. To discover the latter an (18)F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET)/CT examination has been proposed. However, the diagnostic value of a PET/CT in this setting remains unresolved. Thus, we wished to assess the usefulness of a PET/CT study in patients with IE as a supplemental method to standard work-up in evaluating primary and distant infective foci. A retrospective cohort study of 72 IE patients admitted from 2008 to 2010, which had an ¹⁸F-FDG-PET/CT performed. Findings were assessed in relation to the routine work-up, which served as the “gold standard”. One hundred-fifty-nine infectious lesions were identified. ¹⁸F-FDG-PET identified 64 of these, and suggested another 50. Overall sensitivity and positive predictive value was 40 and 56 %, respectively, in detecting both cardiac and extracardiac infective foci. When excluding lungs and organs with high physiological FDG-uptake/secretion, the corresponding values increased to 87 and 52 %, respectively. ¹⁸F-FDG-PET/CT may be an important diagnostic tool in detecting extra cardiac infections in patients with IE, particularly in organs with low physiological glucose uptake.

Keywords Infective endocarditis · Diagnostic · Complications · ¹⁸F-FDG-PET

Introduction

Infective endocarditis (IE) is a well-known and greatly feared entity, with high morbidity and mortality. The clinical presentation and clinical course of IE varies enormously, depending on the comorbidity, the nature of the bacteria and possible complications. One of the major clinical problems in the work up of IE patients is identifying extracardiac manifestations, which might be the portal of entry, the result of embolization, or metastatic infection. The overall embolic rate is estimated to approximately 20–50 %, silent events are noted in 20 % [1]. Therefore, all patients, with IE are subjected to an extensive patient-tailored examination strategy according to international recommendations. Basically, this consists of patient history, physical examination, the use of conventional and/or advanced imaging modalities, and weekly interdisciplinary conferences between cardiologists, microbiologists, surgeons, and infectious disease specialists to optimize the therapeutic management [1, 2].

Currently, the role of (18)F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) in this clinical setting remains unanswered in international guidelines. ¹⁸F-FDG-PET, mainly used in cancer investigation, is a modality with potentially increasing clinical indications. ¹⁸F-FDG, being a radioactive glucose derivate, has predilection for cells with high glucose consumption and makes it non-specific for cancer, infection and inflammation [3]. Combining PET with CT adds an accurate anatomical localization of the metabolic process. However, the on-going assessment of this technique has no standard Ref.

C. Özcan (✉) · A. Asmar · S. Gill · A. C. P. Diederichsen
Department of Cardiology, Odense University Hospital,
Sdr Boulevard 29, 5000, Odense C, Denmark
e-mail: Cengizoezcan@gmail.com

A. Thomassen
Department of Nuclear Medicine, Odense University Hospital,
Odense C, Denmark

[4]. Nonetheless, in clinical practice ^{18}F -FDG-PET imaging has become increasingly used and the preferred method in the diagnosis of unknown infections. This clinical approach is supported by accumulating evidence favouring the use of ^{18}F -FDG-PET imaging as first line imaging approach in patients with certain infectious processes [5].

Since the diagnostic value of ^{18}F -FDG-PET/CT in the setting of IE remains unresolved, we wanted to assess the usefulness of the method as a supplemental method to standard work-up in evaluating primary and distant infective foci.

Method

Study population

This retrospective single centre study comprises 72 patients with definite IE according to Duke's modified criteria [1]. They were admitted to the Department of Cardiology, Odense University Hospital from January 2008 to December 2010 and underwent at least one ^{18}F -FDG-PET/CT. The indication of the ^{18}F -FDG-PET/CT was set by the attending physician. During the same time period another 104 patients with IE were admitted to the department, without having an ^{18}F -FDG-PET/CT performed. The patients' condition varied from critically ill to less severe courses set to conservative strategy or elective surgery. All patients received treatment in accordance to the guidelines from the European Society of Cardiology (ESC). Two physicians (CÖ and AA) were responsible for gathering all relevant and pre-specified data from the medical records. Each case was discussed in the entire study group and in cases with doubt about the clinical relevance of a finding final data was made up as a consensus decision.

^{18}F -FDG-PET/CT scanning

Examinations were conducted on dedicated PET/CT systems (GE Discovery VCT XT, GE Discovery RX or GE Discovery STE; GE Healthcare, Milwaukee, WI, USA). Patients were fasting 6 h (diabetes patients only 4 h) prior to injection and were given a weight adjusted dose of 4 MBq/kg (min 200 and max 400 MBq) ^{18}F -FDG 60 min prior to PET/CT acquisition. The duration of the PET scan was at least 2.5 min per bed position increasing to 3.5 min in extremely overweight patients. Different CT scan protocols were used according to type of disease. Diagnostic scans (≈ 12 mSv) with intravenous contrast media (Iopromide 370 mg iodine/ml) were used when pathological conditions were suspected in the abdomen or in the head/neck region, whereas low-dose CT scans (≈ 5 mSv)

without contrast media were used when pathological conditions were suspected in other regions. The standard field of view for the PET/CT involved the base of the skull to the mid thighs, unless it was specified differently. The analysis of the ^{18}F -FDG-PET/CT for infection and inflammation relied on visual assessment of the distribution and intensity of the tracer. The ^{18}F -FDG-PET was interpreted by two nuclear medicine physicians and the diagnostic CT by a radiologist. A mutual conclusion was achieved.

^{18}F -FDG-PET/CT versus other modalities

Since no gold standard in the work-up of extracardial manifestations in IE exists, the result of each ^{18}F -FDG-PET/CT was compared to the results of the clinical standard work-up according to ESC Guidelines for IE, which at the same time served as gold standard. Depending on the clinical setting, the work-up included patient history, physical examination (including examination by a dentist), laboratory tests, X-ray, CT, ultrasound, magnetic resonance imaging (MRI), nuclear techniques, histopathological studies, microbiological cultures, endoscopies and clinical assistance from other specialities. All patient courses were reviewed weekly at a conference with participants from cardiology, surgery, anaesthesia, infectious disease, and microbiology departments regarding optimizing patient treatment, diagnostics and indication for surgery.

All lesions identified by the ^{18}F -FDG-PET/CT were evaluated, regardless of localization, and the data were described on a per-lesion analysis. This means that any patient could potentially display more than one lesion. A ^{18}F -FDG-PET/CT lesion was considered true positive, if the finding was in agreement with result from other modalities. False positive was defined as a ^{18}F -FDG-PET/CT lesion, which could not be confirmed by the standard work-up. ^{18}F -FDG-PET/CT was classified as true negative, when both ^{18}F -FDG-PET/CT and standard work up showed up negative. False negative was considered to be the result, when ^{18}F -FDG-PET/CT missed a significant lesion detected by the standard work-up. In this study, the imaging modality and/or expert evaluation closest in time to the ^{18}F -FDG-PET/CT were selected for comparison.

Statistical analysis

Data were analysed and compared in order to calculate sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV). Descriptive measures for continuous variables are presented as mean \pm SD or median values and range. Categorical variables are presented as absolute numbers or percentage. Excel software (Microsoft) was used for statistical calculations.

Results

Patient characteristics

The mean age was 63 ± 17 (range 15–89), and 71 % were males. See Table 1 for baseline characteristics. The majority of patients were diagnosed within 1 month from the onset of symptoms, and the ^{18}F -FDG-PET/CT was conducted at a median of 6 days (range 5 days before to 58 days after the diagnosis was established). Left sided IE was seen in the majority of cases. Staphylococci (40 %) and streptococci (29 %) were the most prominent bacteria, as seen in Table 2. Surgery was applied in almost half of the study population (44 %). Valve regurgitation was the main indication for surgery (91 %). In-hospital mortality was 15 %. With a mean follow-up of more than one year (469 days), 6 % had relapse, 3 % reinfection, and long-term survival rate was 72 %.

^{18}F -FDG-PET/CT

Overall study population

A total of 159 lesions were identified by standard work-up and used as reference. ^{18}F -FDG-PET identified 64 of these lesions, and suggested another 50 infectious lesions, that could not be verified by other examinations. The indiscriminating analysis of the overall study population merely showed a sensitivity and PPV of 40 and 56 %, respectively.

Organs with low physiological FDG uptake

When excluding organs with high physiological FDG uptake (central nervous system, heart, and urinary tracts),

Table 1 Patient characteristics

Age (mean) (\pm SD)	63 \pm 17
Male	51 (71)
Diabetes mellitus	12 (17)
Hypertension	26 (36)
Presence or past tobacco use	42 (58)
Heart failure at admission (EF < 50) ^a	15 (22)
Hemodialysis	3 (4)
Immunosuppression	6 (8)
Current i.v. abuse	5 (7)
Congenital heart disease	6 (8)
Previous IE	9 (13)
Valve prosthesis	17 (24)
Native valve regurgitation/stenosis	29 (40)

^a Data based on 67 patients

The values are in mean (\pm SD) or n (%)

Table 2 Type of IE and bacteriology

IE type	
Native valve	52 (72)
Prosthetic valve	12 (16)
Pacemaker/ICD	2 (3)
Vegetation negative	3 (4)
VSD	1 (1)
Other	2 (3)
Microbiological findings	
Staphylococcus aureus	24 (33)
Coagulase-negative staphylococcus	5 (7)
Viridans group streptococci	9 (12)
Streptococcus bovis	0
Other streptococci	13 (18)
Enterococcus species	12 (17)
HACEK	1 (1)
Other bacteria	4 (4)
<i>Escherichia coli</i>	1 (1)
Negative culture findings	3 (4)

The values are n (%)

VSD, ventricular septal defect; Other; combination of both native, prosthesis and lead IE; HACEK, Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella; Other bacteria, Gemella haemolysans, Abiotrophia defectiva, Coxiella burnetii, Granulicatella adiacens

gingiva and the lungs a total of 38 lesions were left. ^{18}F -FDG-PET identified 33 of these lesions but also demonstrated 31 other lesions suggestive of infection or inflammation, leading to a sensitivity and PPV of 87 and 52 %, respectively. For details see Table 3.

False negative results

Compared with MRI, ^{18}F -FDG-PET/CT missed two cases with *spondylodiscitis*. One was misinterpreted as being degenerative changes (Fig. 1), and in the other there was no FDG-uptake. Two cases had an infection with staphylococcus aureus in *the skin*; one had a large infected wound on the finger (Fig. 2), and another had multiple wounds located on face and back. ^{18}F -FDG-PET/CT missed these findings. One false-negative lesion in *the spleen* was diagnosed by a regular CT of abdomen, indicating infarction.

False positive results

In ten patients, variable FDG-uptake was found in *the hip, shoulder, knee, sacroiliac, acromioclavicular and sternoclavicular joints*. However, clinical evaluation based on microbiology, histopathology, X-rays or ultrasonography concluded unspecific findings, thus it was speculated, that all these lesions were non-infectious. Nonetheless, one patient

Table 3 Diagnostic performance of ^{18}F -FDG-PET/CT in detection of extra-cardial manifestations in IE

	N	TP	FP	FN	TN	Sn (%)	Sp (%)	PPV (%)	NPV (%)
All organs		64	50	95		40		56	
Organs with low uptake excluding lungs		33	31	5		87	97	52	
Eyes	72	1	0	0	71	100	100	100	100
Liver	72	4	0	0	68	100	100	100	100
Spleen	72	2	1	1	68	67	99	67	99
Intestinal	72	8	5	0	59	100	92	62	100
Adrenal gland	72	1	0	0	71	100	100	100	100
Genitals	72	0	3	0	69		96	0	100
Vertebra	72	8	0	2	62	80	100	100	97
Vascular vessel	72	1	1	0	70	100	99	50	100
Muscle	72	5	6	0	61	100	91	45	100
Joints	72	1	10	0	61	100	86	9	100
Bones	72	2	4	0	66	100	94	33	100
Orthopedic hardware	72	1	0	0	71	100	100	100	100
Skin	72	0	0	2	70	0	100		97
Lungs	72	18	16	4	34	82	68	53	89
Organs with high uptake or small lesions		13	3	86		13	98	81	
Brain	28	0	0	4	24	0	100		86
Gingiva	63	0	3	22	38	0	93	0	63
Heart	72	13	0	59	0	18		100	0
Kidney	72	0	0	1	71	0	100		99

TP true positive, FP false positive, FN false negative, TN true negative, Sn sensitivity, Sp specificity, PPV positive predictive value, NPV negative predictive value

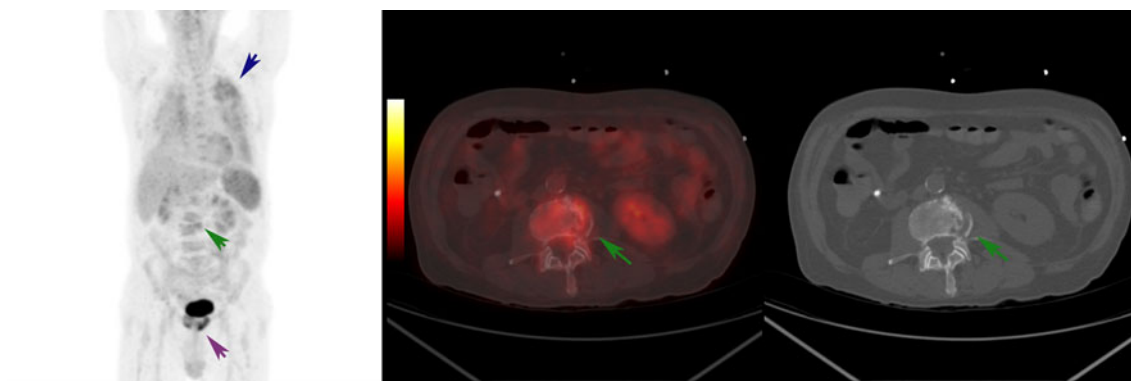


Fig. 1 69-year-old male with prolapsed mitral valve and rupture of chordae. He had a history of rheumatoid arthritis treated with salazopyrine and prednisone. He had diffusely increased FDG-uptake in pulmonary infiltrations, interpreted as pneumonia (TP, blue arrow). There was activation of bone marrow and spleen, probably due to infection. At lumbar level L2/L3, the patient had severe scoliosis and

slightly elevated metabolism, mistakenly interpreted as degeneration (FN, green arrows). Magnetic resonance imaging was indicative of spondylodiscitis but biopsy was never performed. There was inhomogeneous FDG-avidity of the prostate (FP, purple arrow) but neither infection nor malignancy could be verified

with a history of deep venous thrombosis of the right lower limb revealed no signs of infection or inflammation, but ^{18}F -FDG-PET/CT raised suspicion of bursitis of the knee. The patient recovered without further interference (Fig. 3). Additionally six false-positive cases, with FDG-uptake extending from mild to intense hot spots, were seen in the

muscles surrounding the shoulder (Fig. 4), arm, gluteus, pelvic and thighs. Neither clinical evaluation, including ultrasonography, bone scintigraphy, nor microbiological cultures could confirm this. Five patients had various degrees of FDG uptake in the intestinal region (gall bladder, colon, coecum, appendix, sigmoideum, rectum, and anal region).

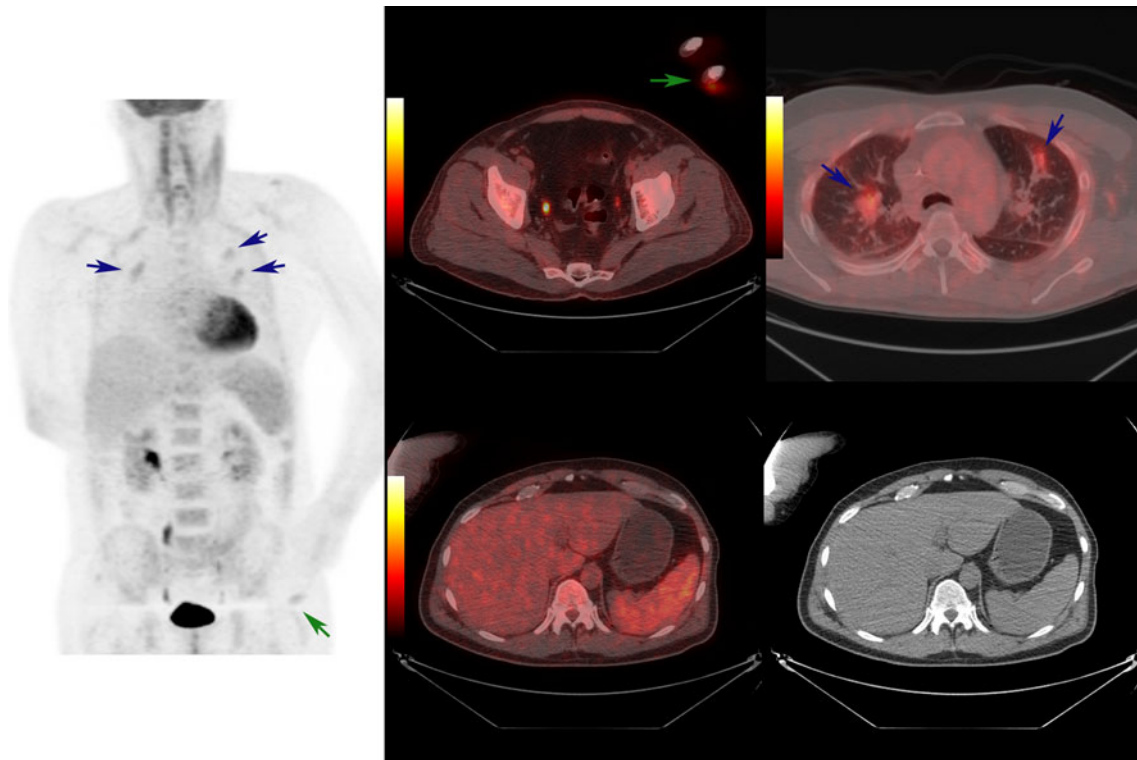


Fig. 2 This 48-year-old male with staphylococcal aortic and mitral valve endocarditis had cut the left fourth finger (FN) on a piece of glass during work. This information was not available when interpreting the ^{18}F -FDG-PET/CT. Retrospectively there was a faint FDG-avidity on the left fourth finger (*green arrows*) which could easily be mistaken by, for instance, urine contamination. The patient also had FDG-avid, localized pulmonary infiltrates (FP, *blue arrows*), which could not be

verified by chest X-ray (which served as standard!). In case-reports similar patterns of FDG-avid pulmonary lesions have been described in septic embolisms. By contrast enhanced CT of the abdomen, two spleen infarctions (FN) were identified and by MR of the brain, infarctions (FN) were demonstrated, both findings were not visualized by ^{18}F -FDG-PET and low dose CT without contrast enhancement. Neither were the infected valves (FN)

Diagnostic endoscopy was normal in three patients. The fourth patient had just a CT verified calcification of the prostate, while in the last case, small amounts of FDG was localized in the appendix, and no supplementary diagnostic procedures were performed. Former *median sternotomy* was associated with four false-positive lesions, where standard clinical judgment disproved infections. Another three patients had increased FDG-uptake in *the genitals*, but all were considered as false-positive; one patient (Fig. 1) had inhomogeneous FDG-uptake in both lobes of prostate. Prostate specific antigen (PSA) was only slightly elevated, also at followed up. The second patient had a similar PSA-level but was never followed up by PSA. The third patient had a faint FDG-uptake in the major labia but no changes by CT—it seemed not to represent urinary contamination and misalignment, though this would be a possible explanation. One patient had indication of a possible abscess in the vicinity of *the iliac artery*, but this was rejected by clinical judgment and more likely sequelae to hemorrhage after invasive angiography. Further one patient had a peripheral FDG-uptake in a *hepatic cyst*, as revealed by ultrasonography. Yet a patient had mild FDG uptake in a wedge shaped

lesion in *the spleen*, but further investigations were not employed.

True positive results

^{18}F -FDG-PET/CT was successful in diagnosing *spondylo-discitis* in eight cases, including one with additional epidural abscess in the lumbar region. ^{18}F -FDG-PET/CT accomplished a sensitivity of 100 % in the *intestinal region* ($n = 8$). Another five cases with hot spots in *the muscles* were true-positive and identified as *psaos abscess* and *abscess in the paravertebral muscle*. Three patients had evidence of relevant *liver* lesions, which were confirmed or suggested by CT and/or ultrasonography. Two patients had *osteomyelitis*, and both were correctly identified by ^{18}F -FDG-PET/CT. One were located to the left clavicle head, and confirmed by MRI, while the other was detected in a diabetic foot and confirmed by X-ray, but missed by bone scintigraphy. Two lesions of significance were diagnosed in *spleen*, where CT of abdomen verified sequela to splenic abscess. Moreover, FDG uptake corresponding to infection was further observed in the *adrenal gland*, *knee prosthesis*

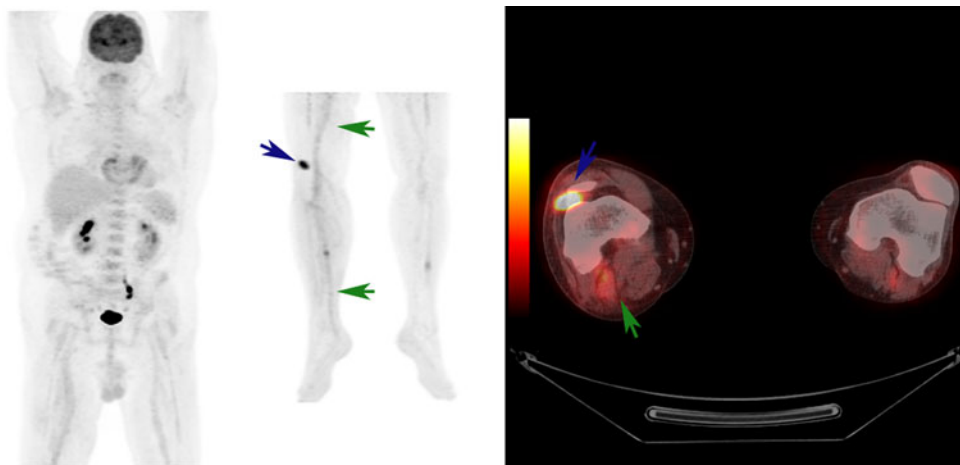


Fig. 3 51-year-old overweight male of 140 kg had a recent history of deep venous thrombosis of the right lower limb (*green arrows*). By ^{18}F -FDG-PET/CT an intensely increased metabolism was demonstrated beneath the right quadriceps tendon and patella, believed to

represent bursitis (FP, *blue arrows*). However aspiration from the knee was never done, and thus the diagnosis never properly established. The patient responded well on antibiotics

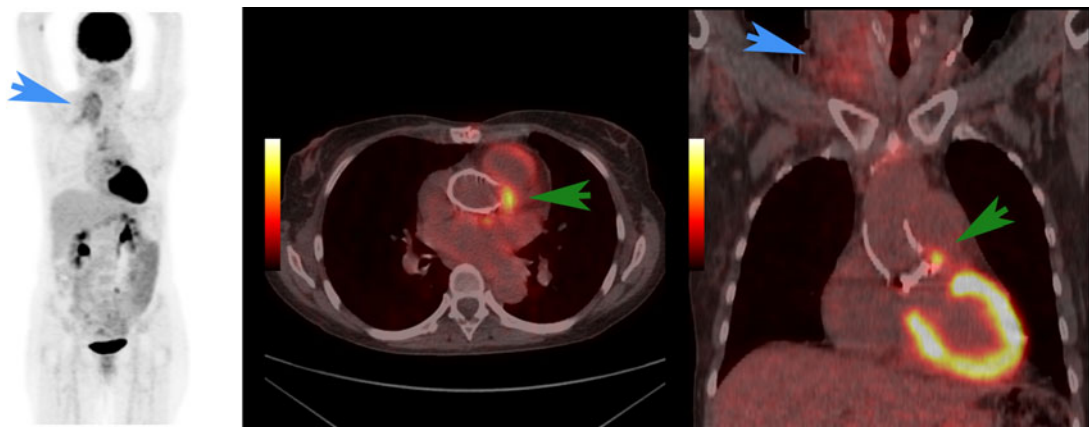


Fig. 4 A 45-year-old female with systemic lupus erythematosus and a prosthetic aortic valve through 1 year was admitted to the hospital with fever of unknown origin and malaise. She was diagnosed with septicemia caused by pneumococci. Transesophageal echocardiography was without signs of infection and was redone after PET/CT, still without proven infection. However, the condition was treated as infective endocarditis. Two years later, she suffered from increasing

periannular leak from the exact location of increased FDG-avidity, clearly demonstrated by ^{18}F -FDG-PET (TP, *green arrow*). She also had a pathological ^{18}F -FDG accumulation in the soft tissue of the neck, misinterpreted as phlegmonous infection of the neck (FP, *blue arrows*). It was most likely a haematoma after removal of central venous catheter

and in a *bifurcational prosthesis* in three different patients. ^{18}F FDG-PET/CT demonstrated also high FDG-uptake in the hip joint in one patient. The only positive finding regarding *the eye* and its surroundings was a basal cell carcinoma on the lateral corner of the left eye.

Pulmonary lesions

Using clinical examination, a plain X-ray and in some cases a CT scan as the reference, the sensitivity and PPV were 82 and 53 %, respectively.

False negative results

Four patients had false-negative *pulmonary* findings. One of these had excessive pleural effusion and atelectasis by ^{18}F -FDG-PET/CT, but no FDG avid pulmonary infiltrates, whereas the other three had neither infiltrates nor FDG-avid lesions.

False positive results

Sixteen patients had *pulmonary* lesions, which could not be confirmed by the clinical judgment or other modalities. In

this context, it is important to acknowledge the inappropriateness of the reference method used.

True positive results

^{18}F -FDG-PET/CT identified 18 of 22 pulmonary lesions diagnosed by X-ray and CT.

Organs with high physiological uptake/secretion and infective cardiac vegetations

The brain, heart, and kidneys are known to have a high physiological FDG uptake or secretion, whereas gingival lesions may go unrecognized by PET, due to partial volume effect, which may also be superimposed by salivary secretion. In these organs the values of sensitivity and PPV were 13 and 81 %, respectively, (Table 3).

False negative results

^{18}F -FDG-PET/CT was not able to detect IE in 59 cases. In a similar way ^{18}F -FDG-PET/CT performed poor in detection of relevant foci in the oral cavity. In all but nine patients, an oral evaluation was performed by a dentist resulting in following diagnosis; Parodontitis apicalis chronica ($n = 5$), Parodontitis marginalis/profund parodontit ($n = 4$), Redix relicta ($n = 1$), Cystis residualis ($n = 1$), ulcus decubitale ($n = 1$), and unspecified dental foci ($n = 10$). Dental extractions were applied in almost all cases. Altogether ^{18}F -FDG-PET/CT had 22 false-negative findings with respect to the oral cavity, particularly the teeth and gums. Stroke events in the form of septic embolism at the time of the ^{18}F -FDG-PET/CT was overlooked in four cases, and this also applied in one patient with infection in the kidney.

False positive results

Three patients showed signs of FDG uptake in the oral cavity, but these were not reproducible by dentist examination.

True positive results

^{18}F -FDG-PET/CT was able to visualize compelling and non-physiological hot spots in the heart (eight prosthetic valve IE, four native valves, and one lead infection), of whom one had no echocardiographic evidence of vegetation and another had newly developed advanced atrioventricular block.

Time from diagnosis until ^{18}F -FDG-PET/CT: early versus late

The median time from diagnosis of IE until performing ^{18}F -FDG-PET/CT was 6 days, and ≤ 6 days was thus taken

as the cut off between early versus late ^{18}F -FDG-PET/CT. In organs with low physiological uptake sensitivity and PPV were 78 % (CI 52–93) and 54 % (CI 34–73), respectively in the early group ($n = 37$), while the values for the late group ($n = 35$) were 95 % (CI 73–100) and 50 % (CI 34–66), respectively, for details see Table 4.

Discussion

A preliminary review conducted by Bertagna et al. [6] reports that ^{18}F -FDG-PET/CT cannot substitute routine investigations in making the final diagnosis of IE, but it might contribute as an added value in evaluating extracardiac infective lesions. In this study, we report the observed results of 72 IE patients undergoing ^{18}F -FDG-PET/CT, the so far largest IE population investigated. Accordingly, our study reported both novel and several intriguing findings. First, the performance of ^{18}F -FDG-PET/CT in identifying extracardiac manifestations of IE in organs with low physiological uptake (like liver, spleen, intestinal, adrenal gland, genitals, vertebra, vascular vessel, muscle, joints, bones, orthopedic hardware, and skin) showed very promising results with a high sensitivity. Second, the ability of ^{18}F -FDG-PET/CT to detect infectious foci in organs with high physiological glucose (including the heart and the valves) uptake is poor. A number of mainly relatively small studies have evaluated the value of ^{18}F -FDG-PET/CT in patients with occult infections, which all showed promising results and in several cases the scanning led to a change in treatment management [7–10]. Riet et al. [11] recently conducted the first prospective and so far, the only study ($n = 25$) to consider the diagnostic role of ^{18}F -FDG-PET/CT in a selected IE population with possible peripheral embolism

Table 4 ^{18}F -FDG-PET/CT performed early (≤ 6 days after admission) versus late (> 6 days)

	TP	FP	FN	Sn (CI) (%)	PPV (CI) (%)
Early PET/CT ($n = 37$)					
All organs ^a	23	13	46	33 (23–46)	64 (46–79)
Low uptake ^a	14	12	4	78 (52–93)	54 (34–73)
High uptake	9	1	42	18 (9–31)	90 (54–99)
Late PET/CT ($n = 35$)					
All organs ^a	23	21	45	34 (23–46)	52 (37–67)
Low uptake ^a	19	19	1	95 (73–100)	50 (34–66)
High uptake	4	2	44	8 (3–21)	67 (24–94)

Low and High uptake denote low and high physiological FDG-uptake organs, respectively; CI, 95 % confidence interval

TP true positive, FP false positive, FN false negative, Sn sensitivity, PPV positive predictive value

^a Excluding lung lesion

or distant infectious lesions. Intubated patients, patients referred to immediate surgery and patients with renal impairment were excluded. An ^{18}F -FDG-PET/CT was performed within 2 weeks from diagnosis. Median age was 70 with a male:female ratio of 3:2 and prosthetic valve IE was observed in 40 %. Maybe as a consequence of the exclusion of groups, staphylococcus aureus rate was low (16 %). The ^{18}F -FDG-PET/CT detected embolization and metastatic infection in 44 % of the study population, 28 % of the findings were occult, whilst only 12 % had FDG uptake around the valves. A therapeutic impact in almost one-third of patients was shown. So far, most experience regarding the benefit of ^{18}F -FDG-PET/CT to distinctively detect the IE (the affected valve) is based on casuistic reports [12]. The diagnostic value of ^{18}F -FDG-PET/CT to establish the diagnosis IE is, however, dubious, since lesions may be small, moving and surrounding myocardium may or may not be FDG-avid and disturbed by attenuations artefact from prosthetic valves. These factors may reduce sensitivity and specificity. This issue is discussed in detail by Bertagna et al. [6].

In line with these studies we demonstrated results favoring ^{18}F -FDG-PET/CT as a supplemental tool in the work up of IE patients with distant infective lesions. As opposed to several of the other studies, we enrolled exclusively patients with IE, including those excluded in the study of Riet et al. Although our study population was a selected subgroup of patients admitted with IE, our patients were still comparable with a European cohort [13]. Another crucial difference is that the results estimated in the abovementioned studies appear to be on a per patient basis, which means that for any PET, the final result was either categorized as TP, FP, TN or FN. In fact PET can often report more than one finding. In an attempt to handle this dilemma we based our estimation on a per lesion basis, hence giving us the benefit of providing with a more accurate result. Moreover, ^{18}F -FDG-PET/CT is not definitively able to distinguish between infection, inflammation and cancer, thus in clinical practice, the final report typically contains a combination of significant, insignificant and often dubious findings. In extension of this, we were aware, that ^{18}F -FDG-PET/CT could identify relevant non-infectious abnormalities. Such findings were cancer in the lungs or skin, which could serve as a portal of entry, and therefore we found it reasonable to include these findings as positive lesions.

In order to improve visualization of the lesions (increase the target-to-background ratio) by ^{18}F -FDG-PET/CT, it has been suggested to reduce time between FDG-injection and imaging. Inflammatory cells, in contrast to malignant cells, have an active glucose-6-phosphatase enzyme resulting in escape of FDG out of the inflammatory cells, thereby increasing the target-signal in early images [14].

Since treatment with antibiotics might diminish the infectious foci, it has been suggested, to perform the ^{18}F -FDG-PET/CT early in the disease course [15]. However, if the scan is performed very early, the lesions might be too small to be detected. In our retrospective study, the ^{18}F -FDG-PET/CT was requested by the clinicians mostly in cases without infection control, giving a relative broad time span. We observed a slightly higher sensitivity among those, who underwent a late ^{18}F -FDG-PET/CT. However, since the early versus late scan was not due to randomisation the observed difference may be a coincidence, and should be investigated further in a randomised study.

It is important to emphasize that, in most cases, ^{18}F -FDG-PET/CT findings are dependent on confirmatory tests as the modality is rather unspecific and PPV is rather low. To clarify the value of ^{18}F -FDG-PET/CT in a clinical setting a randomized trial is warranted. ^{18}F -FDG-PET/CT should be performed on the day of diagnosis, together with other relevant diagnostics modalities to perform a comparative analysis without a time difference. Moreover ^{18}F -FDG-PET/CT should be repeated to elucidate any progress or reduction of the lesions. Clinical endpoints should comprise complications, mortality, and recurrence of IE. Since the lack of a gold standard, a microbiological examination for every finding proposed by ^{18}F -FDG-PET/CT is mandatory, however presently not possible. In the future, molecular imaging visualizing bacteria or their products may help in identifying active endocarditis at an earlier stage at the same time perhaps even reporting the responsible type of bacteria [16].

Limitations

Given the retrospective nature of this work, diagnostic performance of ^{18}F -FDG-PET/CT was per se difficult to estimate because comparison relied on the verification of all lesions by other (sometimes inferior) modalities. No well-defined gold standard could be achieved. Indeed the lesions detected by the ^{18}F -FDG-PET/CT may have been misclassified because of missing microbiological culture. Even if microbiological culture had been recruited in all lesions, errors may have been added by aspiration from necrotic regions, by introducing bacteria accidentally or because of effect of antibiotic therapy. Nonetheless, in most of the 159 lesions identified, needle aspiration was not performed and microbiology not assessed. We therefore made large efforts to confirm every finding by discussing each single case in plenum, and making a consensus decision in cases with doubt. This meant that the standard work up and the clinical diagnose served as the reference standard.

Moreover, clinical assessment, chest X-ray and a CT scan might serve as a poor reference for pneumonia.

However, a tracheal aspiration was only seldom performed. Furthermore, in certain occasions, the diagnosis was based solely on the results of the ^{18}F -FDG-PET/CT, even though it was the experimental test. Although our patients were comparable with the European cohort, this study only involved patients with IE, in whom ^{18}F -FDG-PET/CT was performed (41 % of all patients) and thus the study is not consecutive.

Conclusion

^{18}F -FDG-PET/CT is feasible and yields a promising future in detecting extra cardiac infections in patients with IE, especially when excluding the central nervous system, the dental region, the lungs and the urogenital system. Future prospective studies may reveal its true potential in locating infectious foci, which would spare the patient for additional non-contributing confirmatory imaging.

Conflict of interest The authors declare that they have no conflicts of interest.

References

- Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, de Jesus Antunes M, Thilen U, Lekakis J, Lengyel M, Muller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL (2009) Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the task force on the prevention, diagnosis, and treatment of infective endocarditis of the European Society of cardiology (ESC). Endorsed by the European Society of clinical microbiology and infectious diseases (ESCMID) and the International Society of chemotherapy (ISC) for infection and cancer. *Eur Heart J* 30(19):2369–2413. doi:10.1093/eurheartj/ehp285
- Thuny F, Grisoli D, Collart F, Habib G, Raoult D (2012) Management of infective endocarditis: challenges and perspectives. *Lancet* 379(9819):965–975. doi:10.1016/S0140-6736(11)60755-1
- Kumar R, Basu S, Torigian D, Anand V, Zhuang H, Alavi A (2008) Role of modern imaging techniques for diagnosis of infection in the era of ^{18}F -fluorodeoxyglucose positron emission tomography. *Clin Microbiol Rev* 21(1):209–224. doi:10.1128/CMR.00025-07
- Basu S, Chryssikos T, Moghadam-Kia S, Zhuang H, Torigian DA, Alavi A (2009) Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. *Semin Nucl Med* 39(1):36–51. doi:10.1053/j.semnuclmed.2008.08.004
- Israel O, Keidar Z (2011) PET/CT imaging in infectious conditions. *Ann N Y Acad Sci* 1228:150–166. doi:10.1111/j.1749-6632.2011.06026.x
- Bertagna F, Bisleri G, Motta F, Merli G, Cossalter E, Lucchini S, Biasiotto G, Bosio G, Terzi A, Muneretto C, Giubbini R (2012) Possible role of ^{18}F -FDG-PET/CT in the diagnosis of endocarditis: preliminary evidence from a review of the literature. *Int J Cardiovasc Imaging* 28(6):1417–1425. doi:10.1007/s10554-011-9984-1
- Bleeker-Rovers CP, Vos FJ, Wanten GJ, van der Meer JW, Corstens FH, Kullberg BJ, Oyen WJ (2005) ^{18}F -FDG PET in detecting metastatic infectious disease. *J Nucl Med* 46(12):2014–2019
- Simons KS, Pickkers P, Bleeker-Rovers CP, Oyen WJ, van der Hoeven JG (2010) ^{18}F -fluorodeoxyglucose positron emission tomography combined with CT in critically ill patients with suspected infection. *Intensive Care Med* 36(3):504–511. doi:10.1007/s00134-009-1697-8
- Kluge S, Braune S, Nierhaus A, Wichmann D, Derlin T, Mester J, Klutmann S (2012) Diagnostic value of positron emission tomography combined with computed tomography for evaluating patients with septic shock of unknown origin. *J Crit Care* 27(3):316.e1–316.e7. doi:10.1016/j.jcrc.2011.10.004
- Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PF, van Dijk AP, Cuijpers ML, Adang EM, Wanten GJ, Kullberg BJ, Oyen WJ (2010) ^{18}F -FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. *J Nucl Med* 51(8):1234–1240. doi:10.2967/jnumed.109.072371
- Van Riet J, Hill EE, Gheysens O, Dymarkowski S, Herregods MC, Herijgers P, Peetermans WE, Mortelmans L (2010) ^{18}F -FDG PET/CT for early detection of embolism and metastatic infection in patients with infective endocarditis. *Eur J Nucl Med Mol Imaging* 37(6):1189–1197. doi:10.1007/s00259-010-1380-x
- Vind SH, Hess S (2010) Possible role of PET/CT in infective endocarditis. *J Nucl Cardiol* 17(3):516–519. doi:10.1007/s12350-009-9174-x
- Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falco V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH (2009) Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International collaboration on endocarditis-prospective cohort study. *Arch Intern Med* 169(5):463–473. doi:10.1001/archinternmed.2008.603
- De Winter F, Vogelaers D, Gemmel F, Dierckx RA (2002) Promising role of ^{18}F -fluoro-d-deoxyglucose positron emission tomography in clinical infectious diseases. *Eur J Clin Microbiol Infect Dis* 21(4):247–257. doi:10.1007/s10096-002-0708-2
- Gotthardt M, Bleeker-Rovers CP, Boerman OC, Oyen WJ (2010) Imaging of inflammation by PET, conventional scintigraphy, and other imaging techniques. *J Nucl Med* 51(12):1937–1949. doi:10.2967/jnumed.110.076232
- Panizzi P, Nahrendorf M, Figueiredo JL, Panizzi J, Marinelli B, Iwamoto Y, Keliher E, Maddur AA, Waterman P, Kroh HK, Leuschner F, Aikawa E, Swirski FK, Pittet MJ, Hackeng TM, Fuentes-Prior P, Schneewind O, Bock PE, Weissleder R (2011) In vivo detection of *Staphylococcus aureus* endocarditis by targeting pathogen-specific prothrombin activation. *Nat Med* 17(9):1142–1146. doi:10.1038/nm.2423