ORIGINAL ARTICLE INFECTIOUS DISEASES

# The role of FDG-PET/CT imaging in early detection of extra-cardiac complications of infective endocarditis

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## Abstract

The exact incidence of extra-cardiac complications (ECC) in patients with infective endocarditis (IE) is unknown but presumed to be high. These patients, although mostly asymptomatic, may require a more aggressive therapeutic approach. $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) is used for the diagnosis of infections, but its role in the early diagnosis of IE complications is still unclear. This study aimed to evaluate the role of FDG-PET/CT in the early diagnosis of ECC in IE and its implications for medical management. We prospectively studied 40 consecutive patients with a confirmed diagnosis of IE (according to the modified Duke criteria) who underwent a whole body FDG-PET/CT study within 14 days from diagnosis. The FDG-PET/CT demonstrated ECC in 17 (42.5%) patients, while 8 (38.1%) of them were asymptomatic. The most frequent embolic sites were musculoskeletal and splenic. Owing to the FDG-PET/CT findings, treatment planning was modified in 14 (35%) patients. This included antibiotic treatment prolongation (27.5%), referral to surgical procedures (15%) and, most substantially, prevention of unnecessary device extraction (17.7%). According to our experiences, FDG-PET/CT imaging was useful in the detection of embolic and metastatic infections in IE. This clinical information had a significant diagnostic and therapeutic impact in managing IE disease.



**Keywords:** $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography, complications, embolic events, endocarditis, extra-cardiac

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## Background

The exact incidence of extra-cardiac complications (ECC; e.g. embolic events and metastatic infections) in infective endocarditis (IE) remains unknown, but is considered to be high and reported in 20–50% of patients in various reports [1–3]. Moreover, a substantial percentage of patients remain relatively asymptomatic [4] and present a diagnostic challenge for physicians. Because these patients may also require a different therapeutic approach, prompt diagnosis of embolic complications is essential.

Different imaging modalities have been used for the diagnosis of ECC of IE (e.g. X-rays, ultrasonographic imaging, nuclear scintigraphy, computerized tomography and magnetic resonance imaging). Each imaging modality has its own niche in the detection spectrum of different complications, but none with the ability to provide a comprehensive diagnostic evaluation [5]. In recent years, $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) has emerged as an efficient modality for the identification of neoplastic, inflammatory and infectious processes [6,7]. Several studies have demonstrated the role of FDG-PET/CT in detecting infections of vascular prostheses [8–10] and implantable pacemakers/defibrillators [11–14]. Furthermore, an important role of FDG-



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PET/CT in the diagnosis of IE has been proposed by several recent publications [15–21]. Few data regarding the diagnosis of ECC by FDG-PET/CT exist [22–24]. Therefore, we aimed to assess the role of FDG-PET/CT in diagnosing ECC of IE.

## Methods

### Study population

All consecutive patients (> 18 years old) with a definite diagnosis of IE admitted to our medical centre between May 2010 and July 2013, were included in the study. The definite diagnosis of IE was confirmed using the modified Duke criteria [25]. We excluded clinically unstable patients, patients who required emergency cardiac surgery, patients who were unable to remain in a prone position and patients who were unable or unwilling to provide an inform consent. The study protocol was approved by the institutional review board.

The following data were collected on admission and during the hospitalization for all patients: demographic baseline characteristics, co-morbidities, Charlson co-morbidity index [26], physical examination report, trans-oesophageal echocardiographic (TEE) evaluation, microbiological and laboratory data including serum markers of inflammation (C-reactive protein, rheumatic factor and white blood cell count), course of hospitalization, FDG-PET/CT results and clinical outcomes.

All patients underwent FDG-PET/CT within 14 days from the established diagnosis. Inevitably, all examinations were performed during antibiotic treatment, which was initiated by the treating physicians who were unrelated to the study staff. Nine patients had urgent surgical valve replacement. In six patients the valve replacement was performed before FDG-PET/CT.

All further evaluation, antibiotic treatment type and duration, and reference to surgical procedures were at the discretion of the treating physician, not involved in the study. Additional imaging modalities (e.g. chest X-ray, ultrasound, CT or bone scintigraphy) were performed if indicated and at the discretion of the treating physician.

The FDG-PET/CT findings were categorized into ECC (embolic and distant infection), concomitant infections, potential port of entry and incidental findings. The diagnosis of embolic and distant infections included the following findings: septic infarction and/or metastatic abscess to spleen, brain, kidneys, liver, peripheral vasculature and lung, septic arthritis and spondylodiscitis. Furthermore, we evaluated the impact of FDG-PET/CT findings on the management and clinical outcome according to three categories: effect on antibiotic duration (prolonged or shortened), referral for surgical procedure (excision of infection site, extraction of infected foreign body) or prevention of unnecessary surgical procedures.

Due to the small sample of patients, only descriptive statistics were used to present the results of the study.

### Whole body FDG PET/CT

All patients underwent FDG-PET/CT on a GE Discovery STE Whole Body PET CT scanner (GE Medical Systems, Milwaukee, WI, USA) after 4 h of fasting. Blood glucose levels were examined before $^{18}$F-FDG injection to ensure a blood glucose level < 200 mg/dl. CT images were acquired at 120 kV and 80 mA, pitch 1.75, 0.8 s per tube rotation and slice thickness of 3.75 mm. During whole body CT examination, 80 mL of contrast agent (Ultravist 300, Schering AG, Berlin, Germany) was administered intravenously to ensure fully diagnostic CT data (19 patients with renal failure or iodine allergy underwent CT without contrast intravenous administration). The PET scan was performed 45–90 minutes after intravenous injection of 10–15 mCi of $^{18}$F-FDG. The contrast-enhanced CT was used for attenuation correction of the PET data. PET was performed from head to mid-thigh, 2–3 min per bed position. Resulting in a total PET scan time of approximately 20–25 min (seven or eight bed positions).

Splenic hyperactivity due to infection/haematopoietic reaction was recognized by diffuse increased uptake of FDG in the spleen. Infarct or abscess was recognized by either focal increased or decreased uptake of FDG in the spleen. The latter was considered to be ECC embolic/metastatic to the spleen. An ECC brain finding was considered when either increased or decreased focal uptake was demonstrated compared with the normal brain uptake: increased around abscess and decreased in stroke area.

The images were interpreted by two nuclear medicine and radiology experts who were blinded to the patients' other imaging results.

## Results

We included 40 patients (mean age 58.9 ± 15.8 years, 28 male) with a definite diagnosis of IE who underwent FDG-PET/CT. Baseline demographic characteristics are summarized in Table 1. Eight patients (20%) had prosthetic valve endocarditis (four aortic valve and four mitral valve). Additional predisposing factors for IE included endovascular devices such as implantable pacemakers or defibrillators, left ventricular assist device (LVAD) and arterial lines in 14 patients (35%) (Table 1).

The diagnosis of definite IE was established in 27 patients using two major criteria and in 13 patients using one major and three minor criteria. Eight patients had culture negative endocarditis: two had positive serology for Q-fever and one for *Bartonella*. The other five were probably negative because of previous antibiotic treatment. The blood cultures and other

**TABLE 1. Population study baseline characteristics**

| Characteristics | Total (%) $n = 40$ |
|---|---|
| Baseline characteristics | |
| Age (years) | 58.9 ± 15.8 |
| Gender, men | 28 (70) |
| Diabetes mellitus | 12 (40) |
| Hypertension | 18 (45) |
| Ischaemic heart disease | 9 (22.5) |
| Chronic renal failure | 9 (22.5) |
| Haemodialysis | 3 (7.5) |
| Prior stroke | 3 (7.5) |
| History of cancer | 6 (15) |
| Charlson Score | 3.7 ± 2.6 |
| **Predisposing factors to infective endocarditis** | |
| Prior infective endocarditis | 6 (15) |
| Prosthetic valve/Valve repair | 13 (40.6) |
| Congenital heart disease | 2 (5) |
| Endovascular devices | |
| Aortic graft/Stent | 4 (10) |
| Implantable device (pacemaker/ICD/CRT) | 10 (25) |
| Left ventricular assist device | 1 (2.5) |
| Arterial line (permacath, portacath) | 3 (7.5) |
| Drug abuser | 1 (2.5) |
| Invasive procedure before admission | 9 (22.5) |

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

laboratory characteristics are summarized in Table 2. A pathological conformation for IE was obtained in nine patients who underwent urgent surgical valve replacement.

All patients underwent transthoracic echocardiography (TTE) as well as TEE in their initial evaluation (Table 2). A clear vegetation (mean size 9.8 ± 6.7 mm) was demonstrated by TEE in 26 (65%) patients (eight prosthetic valves, 15 native valves and three implantable device electrodes). Two patients were diagnosed with perivalvular abscess and four (10%) had a new valvular insufficiency. The remaining eight (20%) patients had no evidence for IE by echocardiography (TEE) imaging.

**TABLE 2. Blood cultures, laboratory data and echocardiographic findings**

| Laboratory data | Total (%) $n = 40$ |
|---|---|
| **Bacterial pathogens** | |
| *Streptococcus viridans* | 4 (10) |
| *Staphylococcus aureus* | 8 (20) |
| *Streptococcus* spp. | 6 (15) |
| *Enterococcus faecalis* | 5 (12.5) |
| HACEK | 2 (5) |
| *Coxiella burnetii* | 2 (5) |
| *Listeria* spp. | 1 (2.5) |
| *Bartonella* spp. | 1 (2.5) |
| CoNS | 4 (10) |
| *Propionibacterium acnes* | 1 (2.5) |
| *Diphtheroids* spp. | 1 (2.5) |
| **Echocardiographic findings-** | |
| Vegetation on prosthetic valve | 8 (20) |
| Vegetation on native valve | 15 (37.5) |
| Perivalvular abscess | 2 (5) |
| New valvular insufficiency | 8 (20) |
| Vegetation on electrode | 3 (7.5) |
| No findings | 4 (10) |
| Vegetation size (mm) | 9.8 ± 6.7 |
| **Laboratory results –** | |
| White blood cell count (K/μL) | 13.3 ± 8.7 |
| Serum creatinine (mg/dL) | 1.4 ± 1.0 |
| Serum C-reactive protein (mg/dL) | 13.7 ± 8.6 |

Abbreviations: CoNS, coagulase-negative staphylococcus; HACEK, *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.

All patients underwent whole body FDG-PET/CT shortly after the diagnosis of definite IE was established with a median time of 5 days from diagnosis (range 1–14 days) and a median duration of 7 days from antibiotic treatment initiation (range 2–20 days).

### Extra-cardiac FDG-PET/CT findings

Thirty out of 40 (75%) patients had relevant extra-cardiac findings on FDG-PET/CT examination. Embolic/metastatic ECC was evident in 17 patients (42.5%), with musculoskeletal and splenic being the most frequent embolic sites (Table 3). Eight of these patients (38.1%) were asymptomatic at the time of diagnosis. Examples for images of metastatic infections are shown in Figs. 1 and 2. A concomitant infection was demonstrated in 12 (30%) patients (Table 3). A possible portal of entry for infection was detected in four (10%) patients. Non-infectious (incidental) findings were demonstrated in six (15%) patients. In two patients a colonic polyp/mass was demonstrated with PET/CT and diagnosed as malignant adenoma with colonoscopy in both cases (Fig. 3a,b).

### Cardiac findings

Six patients underwent imaging following urgent valve replacement, so we evaluated only 34 patients for the evidence of valvular IE by FDG-PET/CT. Positive FDG intake was demonstrated in only two (5.9%) patients, both with prosthetic valves. The two cases of perivalvular abscess that were diagnosed in TEE were not demonstrated by FDG-PET/CT. In addition, a positive FDG intake was well demonstrated on one of three infected pacemaker electrodes and in three infected aortic grafts/stents (Table 3).

**TABLE 3. Study cohort $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) findings**

| FDG-PET/CT findings | Total (%) $n = 40$ |
|---|---|
| **Extra-cardiac** | |
| Embolic/metastatic infection | **17 (42.5)** |
| Lung | 1 |
| Splenic | 7 |
| Brain | 5 |
| Musculoskeletal | 8 |
| Liver | 3 |
| Concomitant infections | **12 (30)** |
| Pneumonia | 10 |
| Osteomyelitis of the foot | 1 |
| Sternitis | 1 |
| Non-infectious findings | **6 (15)** |
| Colon mass/polyp | 3 |
| Thyroid gland nodule | 2 |
| Lung nodules | 1 |
| Possible portal of entry | **4 (10)** |
| New implanted epicardial lead | 1 |
| Colonic polyp (*Streptococcus bovis* bacteraemia) | 1 |
| Diabetic foot—osteomyelitis | 1 |
| Infected line | 1 |
| **Cardiac/vascular** | |
| Valvular | 2/34 (5.9) |
| Implantable device electrode | 1/40 (2.5) |
| Ascending aorta graft/stent | 3/40 (7.5) |

Numbers are for PET findings (a patient may have had more than one finding).

 

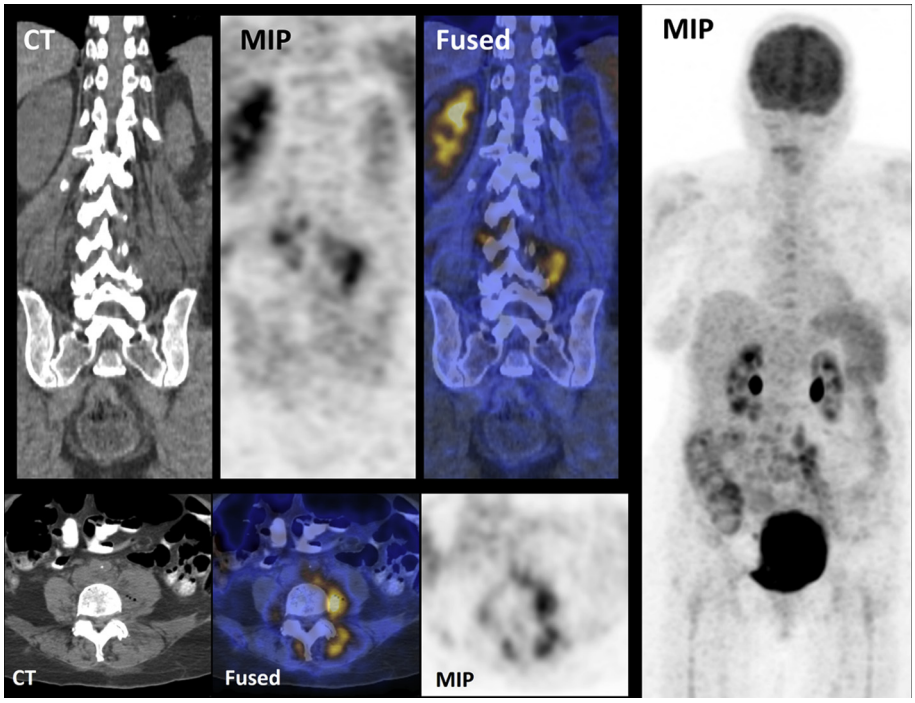


**FIG. 1.** Example of positive $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) for extra-cardiac metastatic infection in a 66-year-old women with *Staphylococcus aureus* infective endocarditis demonstrates a psoas muscle (left) and paraspinal abscess. The FDG-PET/CT images are presented as sagittal and cranial sections in CT, fused and attenuation-corrected maximal intensity projection images.

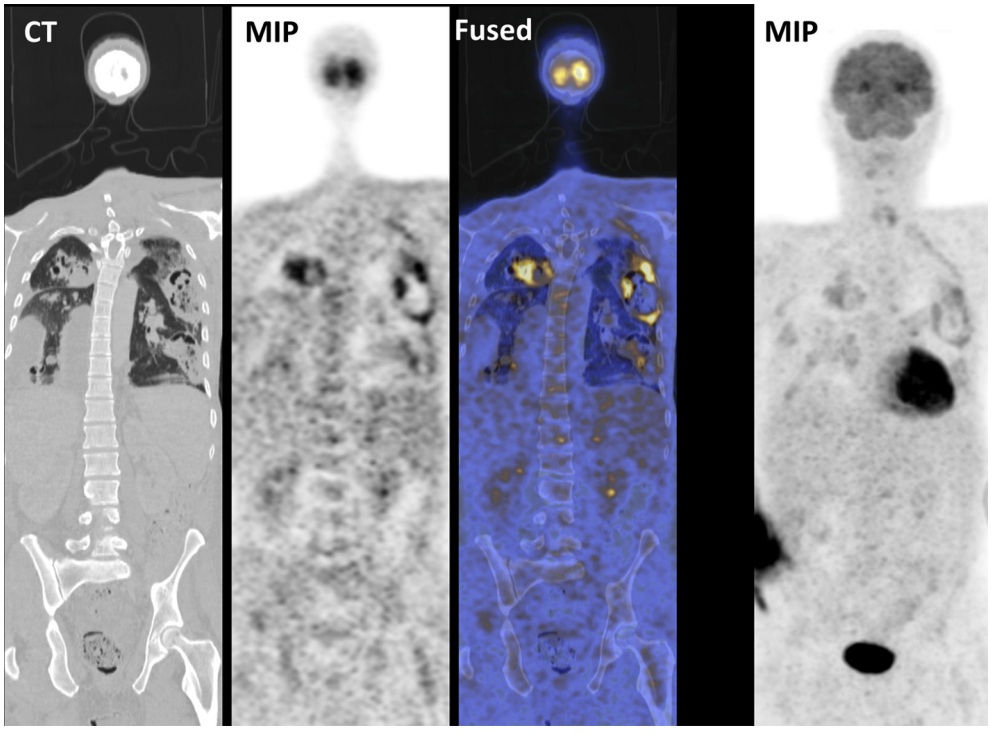


**FIG. 2.** Example of positive $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) for extra-cardiac metastatic infection in a 44-year-old drug abuser with right-sided infective endocarditis demonstrates bilateral lung cavitary infections. The FDG-PET/CT images are presented as cranial sections in CT, fused and attenuation-corrected maximal intensity projection images.

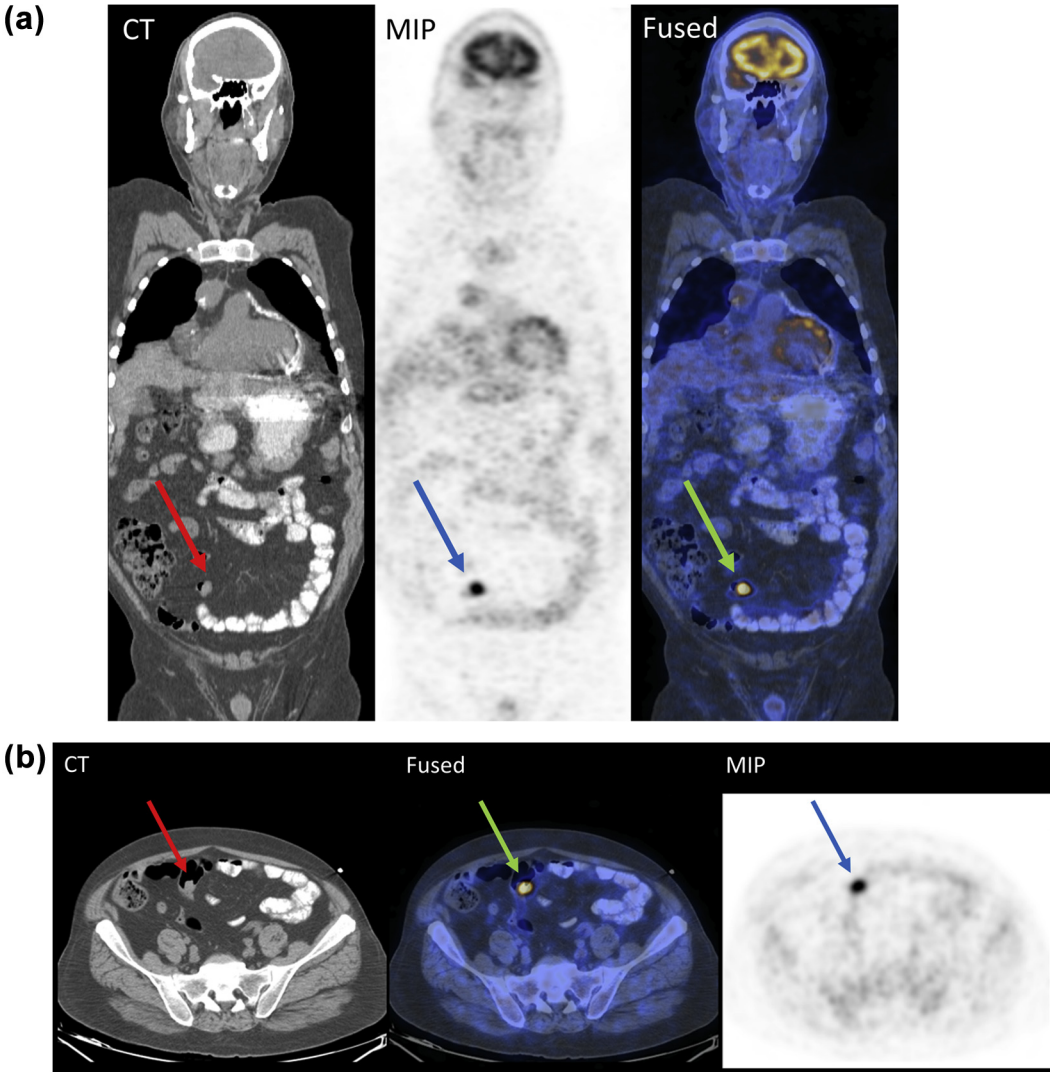


**FIG. 3.** Example of positive $^{18}$fluorodeoxyglucose–positron emission tomography/computed tomography (FDG-PET/CT) for extra-cardiac finding in a 60-year-old man with left ventricular assist device and *Streptococcus bovis* infective endocarditis. The FDG-PET/CT shows an abnormal uptake in the right colon (arrow), revealing a neoplasm that was confirmed as villous adenoma by colonoscopy and no uptake around the device. This finding was presumed to be the port of entry for the bacteraemia. The FDG-PET/CT images are presented as cranial (a) and sagittal (b) sections and in CT, fused and attenuation-corrected maximal intensity projection images.

### Clinical outcome and FDG-PET/CT impact on management

During hospitalization, nine (22.5%) patients required urgent valve replacement and ten (25%) patients required surgical excision of infected locus or infected foreign body. The mean antibiotic treatment duration (excluding Q fever IE) was 6.1 ± 2.1 weeks. The treatment plan was significantly altered in 14 out of 40 (35%) patients owing to the FDG-PET/CT findings. Antibiotic treatment was prolonged in 11 (27.5%) patients as the result of detection of embolic infections by the FDG-PET/CT. Six (15%) patients were referred to surgical procedures (excision of infected locus or infected device) as the result of FDG-PET/CT findings. Additionally, unnecessary device extraction was avoided in three patients (two patients with implantable device and one patient with LVAD) owing to the FDG-PET/CT results with an excellent clinical outcome and no recurrence of documented infection or requirement for device removal at a later time.

## Discussion

Our study demonstrated several important findings regarding the use of FDG-PET/CT imaging in patients with definite IE: primarily, relevant extra-cardiac findings on FDG-PET/CT were demonstrated in the majority of patients (75%). The

 

information obtained by a single FDG-PET/CT examination was useful for the diagnosis of ECC, determination of the source of infections and concomitant infections leading to important changes in the course of the treatment strategy. Given the interpretation of FDG-PET/CT, significant therapeutic changes were made in more than one-third of our patients. However, the role of FDG-PET/CT in the demonstration of cardiac lesions was very limited and much inferior to TEE.

Early diagnosis of ECC has important therapeutic implications [27–29] but may be extremely challenging because of the lack of characteristic symptoms and the need for several imaging modalities to perform a comprehensive evaluation [5]. In our study, we have demonstrated a rate of over 40% of ECC in patients who were already managed with antibiotic treatment. These findings, which have significant implications for clinical management, may have been overlooked through the lack of extra-cardiac symptoms. Currently, there are no specific recommendations for routine ECC evaluation and different modalities are being used according to specific symptoms. By performing a whole body FDG-PET/CT, we completed a rapid comprehensive evaluation using a single diagnostic modality. Taking into account bureaucratic and technical factors we estimate that the time required to perform the necessary evaluation using several different modalities to obtain the same diagnostic findings as FDG-PET/CT would be an average of 7–8 days as opposed to 2–3 days, respectively.

Nowadays, the evaluation of IE has become even more challenging as the result of the extensive use of emerging new intravascular and intra-cardiac devices. Permanent implants provide a continued source of bacteraemia but may impair diagnosis with echocardiography through the appearance of mechanical artefacts. FDG-PET/CT has been shown to have an important role in diagnosis of infected devices [11–14]. Furthermore, FDG-PET/CT contributed to the decision-making process when device removal was considered. For example, a patient with LVAD and *Streptococcus bovis* endocarditis who underwent FDG-PET/CT had no evidence for LVAD apparatus infection (Fig. 3). However, a malignant colonic polyp was demonstrated and subsequently resected and verified as villous adenoma. The unnecessary LVAD extraction was prevented with a complete eradication of the infection and with no further requirements for interventions over a 1-year follow up. The role of FDG-PET/CT in this setting has been demonstrated in the literature, although only in case reports or small case series [30].

Another important finding was the significant impact of FDG-PET/CT findings on therapeutic decisions. In more than 30% of patients the treatment plan was altered according to the FDG-PET/CT findings. Especially important were the surgical procedures that were performed and the unnecessary device extraction that was prevented owing to the FDG-PET/CT findings. Undoubtedly, FDG-PET/CT can provide considerable information used for risk stratification and in the decision-making process for treatment strategy planning in selected cases where the diagnosis of IE is uncertain or when involvement of implantable devices is suspected.

The role of FDG-PET/CT in the diagnosis of valvular endocarditis has been suggested by several small studies and sporadic case reports; however, with some controversy [15–21]. This controversy most probably derives from the lack of a standardized protocol for myocardium imaging with FDG-PET/CT. Several authors [31,32] suggested a protocol where patients were instructed to maintain a very low carbohydrate and fat-rich diet a day before the imaging. The optimal duration of fasting to reduce myocardial FDG uptake is yet to be determined. Our study demonstrated disappointing results regarding the ability of FDG-PET/CT to identify intra-cardiac infected structures. Since our study was designed to investigate mainly the extra-cardiac complications, we used the standard protocol for whole body FDG-PET/CT, which could theoretically explain the low cardiac detection rate. We suggest that the role of FDG-PET/CT in the diagnosis of valvular endocarditis should be further evaluated with an established standardized protocol.

As mentioned, few data exist on the role of whole body FDG-PET/CT in the diagnosis of ECC comprising very small studies with differing study designs. Van Riet et al. [22] evaluated 24 patients with definite endocarditis and demonstrated an ECC rate of 44% using FDG-PET/CT. Our study, which was larger, demonstrated a slightly higher detection rate. The study of Bonfiglioli et al. [23] included 71 patients with suspected endocarditis with an ECC detection rate of only 24%. Recently, Bertagna et al. [24] investigated the role of FDG-PET/CT in diagnosis of prosthetic valve endocarditis in 72 patients with suspected endocarditis. ECC were detected in only eight patients. The higher detection rate in our study could be explained by the well-defined population with a definite diagnosis of IE and possible discrepancies in definitions of extra-cardiac complications between the studies.

## Limitations

Our study has several limitations: this is a single centre study with a relatively small population sample. We did not perform a systematic comparison of the FDG-PET/CT findings to other diagnostic modalities. One of our intentions was to investigate the impact of FDG-PET/CT findings on patient management, so we avoided any interference with the patient evaluation and treatment plan. We aimed to perform our study as close as possible to the accepted common practice in IE. For ethical

reasons, we were limited to a single FDG-PET/CT examination and we could not postpone the initiation of antibiotic treatment until after the examination was performed. Consequently, it is possible that we have underestimated the true incidence of ECC. Furthermore, we could not perform additional standard imaging to compare our FDG-PET/CT results to the reference standard because of the substantial extra radiation exposure.

## Conclusions

FDG-PET/CT was useful for detection of embolic and metastatic infections in IE patients. The potential benefit for FDG-PET/CT imaging in the evaluation of IE derives from its ability to provide simultaneous important data regarding embolization and metastasis of infection to distant organs, possible portal of entry of the infection and evidence for foreign body involvement. All of this essential information has significant impact on diagnosis and treatment planning. Our study results reinforce the results of previous studies, suggesting a role for FDG-PET/CT in the evaluation of patients with IE. The potential role of FDG-PET/CT in the evaluation of patients with IE should be further evaluated in larger cohort studies.

## Transparency Declaration

The authors declare that they have no conflicts of interest.

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