Diagnostic yield of FDG positron-emission tomography/computed tomography in patients with CEID infection: a pilot study

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Aims
Whole body imaging with 18F-fluorodeoxyglucose positron-emission tomography/computed tomography (FDG PET/CT) has proven useful in various infectious diseases. The purpose of this pilot study was to assess the diagnostic yield of FDG PET/CT in patients with cardiac implantable electronic device (CIED) infection.

Methods and results
A total of 21 patients with CIED infection were prospectively included. Diagnosis of CIED infection was made in accordance with current criteria. It was classified in three categories, i.e. superficial skin infection, pocket site infection, or cardiac device-related infective endocarditis (CDRIE). All patients underwent FDG PET/CT. Scans were interpreted blindly, i.e. without prior knowledge of diagnosis, by experienced nuclear medicine physicians. The accuracy of FDG PET/CT was assessed for each diagnostic category. Findings demonstrated superficial skin infection in 1 patient, pocket site infection in 15, and CDRIE in 13 (definite: 7; possible: 6). In patients with pocket site infection, the sensitivity and specificity of FDG PET/CT were 86.7% [59.5–98.3, 95% confidence interval (CI)] and 100% [42.1–100, 95% CI]. The only patient with superficial skin infection was accurately identified by FDG PET/CT. The sensitivity and specificity of FDG PET/CT in patients with CDRIE were 30.8% [9.1–61.4, 95% CI] and 62.5% [24.5–91.5, 95% CI]. Most false-negative results occurred in patients who had undergone previous antimicrobial treatment.

Conclusion
This study indicates that FDG PET/CT is highly accurate for the diagnosis of skin and pocket CIED infection but low for infective endocarditis. This suggests that the reliability of FDG PET/CT findings in management decision making varies according to the type of CIED infection.

Keywords
Cardiac implantable electronic device • Pacemaker • Defibrillator • Infection • Endocarditis • FDG PET/CT

Introduction
Despite advances in technology and standardization of protocols, infections related to cardiac electronic implantable devices (CIEDs) appear to be on the rise and are associated with substantial morbidity and mortality.1–3 Clinical presentation is highly variable and can be misleading. Treatment depends on the extent of infection. In most cases, complete hardware removal followed by prolonged antimicrobial treatment is required. However, in the case of superficial skin or incision infection without hardware involvement, lead and device removal is not necessary.4 Thus, there is a need for diagnostic tools allowing distinction between isolated skin infection and hardware infection. Whole body imaging with 18F-fluorodeoxyglucose (FDG) positron-emission tomography/computed tomography (FDG PET/CT) was first used in oncology but has also proven useful in patients with...
What’s new

- We confirm that, in patients with cardiac implantable electrical devices, $^{18}$F-fluorodeoxyglucose positron-emission tomography/computed tomography is highly accurate for the diagnosis of skin and pocket infection.
- Accuracy of $^{18}$F-fluorodeoxyglucose positron-emission tomography/computed tomography for cardiac device-related infective endocarditis diagnosis is low.
- The reliability of $^{18}$F-fluorodeoxyglucose positron-emission tomography/computed tomography findings in management decision making may therefore vary according to the type of cardiac implantable electronic device infection.

Materials and methods

Patients

All consecutive patients admitted to our tertiary hospital for CIED infection from June to October 2010 were prospectively enrolled in the study. Upon admission, the patient’s medical history and clinical status were determined. Laboratory testing included complete blood counts, search for inflammation markers, and at least three sets of blood cultures after discontinuation of any antimicrobial therapy. Transthoracic and transoesophageal echocardiography (TTE and TEE) were performed as previously described. A multidetector pulmonary CT scan or ventilation-perfusion scintigraphy was performed to screen for septic emboli. If peripheral infection sites were suspected, appropriate investigations were performed. In addition to this standard workup protocol, all patients underwent an FDG PET/CT as described in the next section.

Diagnosis and treatment were defined solely on the standard protocol without taking into account FDG PET/CT findings. Cardiac implantable electronic device infection was classified in current diagnostic categories in accordance with previously described criteria. Superficial skin infection was defined as infection limited to skin or suture. Pocket infection was defined as the presence of frank local inflammatory or infectious signs or exposure of hardware through the skin. Cardiac device-related infective endocarditis (CDRIE) was classified as definite or possible according to standard criteria. In the presence of a lead vegetation, clinical evidence of a local device infection was considered a major criterion for the diagnosis of CDRIE. Lead culture was considered a major criterion only in the absence of a pocket infection or when leads were removed via a remote incision. Blood cultures positive for typical endocardial pathogens or persistently positive bacterial cultures consistent with CDRIE were also considered major criteria.

Complete hardware removal was attempted in patients with CDRIE or pocket infection. The primary approach consisted of endovascular lead extraction. In all cases, cultures of material from the device pocket, generator, and leads were performed. Identification of microorganisms was performed by the conventional phenotypic technique (Vitek®, Biomérieux, France) and by direct analysis of whole cells using MALDI-TOF mass spectrometry (Microflex®, Bruker Daltonics, Germany). Customized antimicrobial regimens were defined by an infectious disease specialist in collaboration with a cardiologist.

The study protocol was approved by our local institutional review board. All participating patients provided written informed consent.

Fluorodeoxyglucose positron-emission tomography/computed tomography

All patients underwent FDG PER/CT in resting state after an 8 h fasting period. Glycaemia was determined to be <9 mmol/L at the time of study. After intravenous administration of 4 MBq/kg of $^{18}$FDG, whole body imaging from the base of the skull to the top of the femoral bones was performed using a GE Discovery ST PET/CT (General Electric Medical System) in the three-dimensional (3D) mode. The CT phase was performed first from the femoral head level using the following acquisition parameters: 140 keV, 80 mA, and 5 mm slice thickness. Once CT imaging was completed, PET acquisition was performed at a rate of 3 min per step. Data were reconstructed by the iterative method (algorithm OSEM) using CT data for attenuation correction. Recorded images were displayed on a Xeleris® workstation (GE Medical System, Waukesha, USA) allowing 3D volume viewing and transaxial, sagittal coronal plane slices. The patient’s radiation dose was about 18 mSv.

Visual and quantitative analysis of FDG PET/CT acquisitions were performed blindly, i.e. without prior knowledge of clinical and bacteriologic findings, by two experienced nuclear medicine physicians (S.C., O.M.). After a quality-control step based on maximum intensity projection analysis, visual analysis was performed on attenuation-corrected and non-attenuation-corrected images and after fusion with CT slices for each data set. Based on the presence and intensity of hotspots around the device and/or leads, the interpreting physician classified the case as positive or negative for generator-pocket infection, superficial infection, or CDRIE. Hotspots other than those associated with the device were observed and noted by the interpreting physician.

Quantitative analysis was performed on attenuation-corrected and non-attenuation-corrected images. The maximal standard uptake value ($\text{SUV}_{\text{max}}$) of $^{18}$FDG was measured on the skin or muscle side of the generator and on any lead hotspot. In all cases, $\text{SUV}_{\text{max}}$ was also measured in a region of interest on the generator pocket, contra-lateral prepectoral region (even if there was no hotspot), descending thoracic aorta, and liver.

Statistical analysis

Continuous variables were expressed as means ± standard deviation and nominal variables as numbers and percentages. Nominal variables were compared using the Fisher’s exact test. The diagnostic accuracy of FDG PET/CT was assessed by calculating sensitivity (percentage of true positive cases identified) and specificity (percentage of true negative cases identified) with associated 95% confidence intervals (CIs). Concordance between FDG PET/CT and current diagnostic categories was quantified by the kappa test. All statistical tests were two sided and $P$ values $<0.05$ were considered as statistically significant. Analyses were performed using R free software (version 2.12, R Development core team). $\text{SUV}_{\text{max}}$ cut-off values for positive diagnosis of CIED infection were assessed using receiver operating characteristics curves.

Results

Diagnostic findings and treatment outcome

Twenty-one patients were prospectively included in this study. There were 14 males and 7 females with a mean age of 68.5 ±
Mean injection time was 72 ± 2.09 min (range, 1–4) leads implanted per patient for 9.8 ± 8.5 years (range, 1–32). Two patients had only abandoned leads in their pockets. The last intervention on the device had been performed for 2.3 ± 1.5 years (range, 1–7) before inclusion in the study. One patient had superficial incision infection and 15 had signs of pocket infection (isolated pocket infection in 7, associated with CDRIE in 8). Diagnosis was CDRIE in 13 patients (definite in 7 and possible in 6). Vegetations were found on leads in 10 patients. Mean vegetation size was 13.7 ± 5.5 mm (range, 6–23 mm). Three patients had vegetations <10 mm. No patient presented a remote infection site.

All 20 patients with pocket infection and/or CDRIE were considered for lead removal. However, explantation could not be performed in one patient with an extravascular lead due to surgical contraindications. The patient with superficial skin infection was not considered for hardware removal. Complete transvenous lead extraction was successful in the 19 patients in whom it was attempted.

Eleven patients were undergoing antimicrobial therapy before inclusion in the study. In eight of these patients, therapy was discontinued for 8.1 ± 8.6 days (range, 1–26) prior to FDG PET/CT. In the remaining three patients, antimicrobial therapy had to be continued due to the severity of infection. Blood cultures were positive in seven patients (33%). The offending microorganisms were Staphylococcus aureus in five patients and Staphylococcus epidermidis in two. Cultures of explanted material were positive in 12 patients (63%). The offending microorganisms were S. aureus in three, S. epidermidis in seven, Staphylococcus capitis in two, Staphylococcus hominis in one, and Propionibacterium acnes in three.

**Yield of fluorodeoxyglucose positron-emission tomography/computed tomography**

Mean injection time was 72 ± 2.2 min (range, 45–140) and mean glycaemia at time of FDG PET/CT acquisition was 5.20 ± 1.11 mmol/L (range, 3.85–7.92). Table 1 summarizes the results of conventional workup and FDG PET/CT. Table 2 summarizes data on diagnostic accuracy of FDG PET/CT.

FDG PET/CT found a total of 20 hotspots on device hardware (13 in the pocket site and 7 along the leads) and 1 hotspot on skin tissue. For diagnosis of superficial skin infection and pocket site infection, visual analysis was accurate in 19 patients. Thirteen patients with hotspots in the pocket site were true positives. Six patients with no hotspot in the pocket site were true negatives. There were two false negatives including one patient whose bacteriological cultures after device extraction were negative. In the patient with superficial skin infection, a hotspot was found in the subcutaneous region of the pocket site scar. This patient, who had been implanted 2 months before, was successfully treated with local antibiotics. There were no false positives. The sensitivity and specificity of visual analysis of FDG PET/CT for detection of pocket or skin infection were 86.7% [59.5–98.3, 95% CI] and 100% [42.1–100, 95% CI], respectively, with a kappa coefficient of 0.79 [0.51–1, 95% CI]. For diagnosis of CDRIE, visual analysis of FDG PET/CT was accurate in nine patients with four true positives (hotspot on intracardiac segment of lead in one patient, on the intravascular segment in two, and on both intracardiac and intravascular segments in one), and five true negatives. There were nine false negatives and three false positives (hotspot on the intracardiac segment of lead in one patient, intravascular segment in one, and extravascular part segment in one). Eight of the nine false negatives had received antimicrobial therapy. Only one of the four patients who had not received antimicrobial therapy was a false negative. The sensitivity and specificity for diagnosis of CDRIE were 30.8% [9.1–61.4%, 95% CI] and 62.5% [24.5–91.5, 95% CI], with a negative kappa coefficient of −0.06 [−0.45 to 0.33, 95% CI].

Quantitative analysis for diagnosis of pocket infection was based on cut-off values obtained by measuring SUVmax in the generator pocket and at pre-selected locations. On attenuation-corrected images, an SUVmax ≥ 1.21 in the pocket or an SUVmax generator pocket/SUVmax contralateral prepectoral region ratio ≥ 2.1 each had a sensitivity of 93.3% and a specificity of 83.3%. On non-attenuation-corrected images, an SUVmax generator pocket/SUVmax contralateral prepectoral region ratio ≥ 1.06 had a sensitivity and a specificity of 100%. SUVmax on leads was not analysed because of the low sensitivity and specificity of visual analysis in detection of CDRIE. In addition to diagnosis of CIED infection, visual analysis of FDG PET/CT allowed detection of breast cancer in two patients including one with bone metastasis (hotspot on rib).

**Discussion**

The most interesting finding of this study involves the high sensitivity and specificity of FDG PET/CT for diagnosis of skin and pocket infection in patients implanted with CIED. However, accuracy for CDRIE was low. To our knowledge, few studies have been specifically designed to evaluate the diagnostic accuracy of FDG PET/CT in patients with definite diagnosis of CIED infection. Several case reports have shown that FDG PET/CT can confirm cardiac device infection by highlighting hotspots on leads or devices15–18 or infective endocarditis (IE) on native or prosthetic valves.19,20 Van Riet et al.21 reported the utility of FDG PET/CT for detection of asymptomatic septic emboli and metastatic infection in patients with IE. Only three prospective studies have focused on FDG PET/CT for assessment of CIED infection.4,22 In a different patient population with suspected CIED infection, Bensihmon et al.22 obtained results consistent with ours regarding pocket site infection. Diagnostic yield was good for device infection and poor for lead infection. Ploux et al.8 demonstrated the value of FDG PET/CT for diagnosis of lead infection in patients with unexplained fever and negative TEE and blood cultures. In a recent study in which suspected device infection was confirmed in 35 out of 42 patients, Sarrazin et al.23 concluded that FDG PET/CT was highly sensitive and specific for CIED infection. Unlike us, however, Sarrazin et al. did not differentiate the diagnostic yield for pocket and lead infection since only 52% of their patients had a TEE.
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical presentation</th>
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<th>Lead vegetations (size, mm)</th>
<th>Blood culture</th>
<th>Hardware culture</th>
<th>Diagnosis</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td>CDRIE</td>
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<td>Positive</td>
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<td>Pocket infection + CDRIE (possible)</td>
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<td>Positive</td>
<td>CDRIE (possible)</td>
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</table>

CDRIE, cardiac device-related infective endocarditis; NA, not applicable.
Prior antimicrobial therapy and/or vegetation size could account for the poor sensitivity of FDG PET/CT in our patients with CDRIE. Antimicrobial treatment is known to lower the affinity of FDG. This effect is of great clinical importance since many patients with suspected CDRIE receive antibiotics before referral to specialized centres as was the case for 9 of the 13 CDRIE patients in the present study. Further study is needed to determine the lapse of time necessary to optimize diagnostic accuracy after discontinuation of antimicrobial therapy. The second factor possibly implicated in poor sensitivity in CDRIE patients is the possibility of vegetation size being lower than the spatial resolution of FDG PET/CT. High FDG uptake in normal heart tissue may explain why low-intensity lesions go undiagnosed. In this study, one of the three false-positive CDRIE patients had a lead with an extravascular course that might have accounted for the observed hotspot. Diagnosis was also questionable in another ‘false-positive’ patient who experienced an ischaemic stroke during endovascular lead extraction. Thus, septic embolus through a patent foramen ovale cannot be ruled out.

In this study, two false negatives involved patients with pocket site infection. In one of these patients, all bacteriological cultures including blood, pocket tissue, generator, and lead cultures were negative despite no prior antimicrobial therapy. In this regard, it should be underlined that conventional diagnosis of pocket infection in clinical practice is based mainly on judgement and that this lack of gold standard is clearly a limitation for evaluation of a new diagnostic method. Interestingly, diagnosis of superficial skin infection based on clinical judgement in the second patient was confirmed by FDG PET/CT that demonstrated hotspots only in the subcutaneous region. In the study of Sarrazin et al., superficial skin infection was suspected based on PET/CT scan in seven patients including six that were successfully treated using a conservative approach.

Although beyond the direct scope of study, it is interesting to note that whole body FDG PET/CT detected two breast cancers including one with bone metastasis. Since standard pulmonary imaging did not detect pulmonary septic embolism, it was not possible to evaluate the performance of FDG PET/CT for diagnosis of septic metastasis.

### Limitations

The small number of patients obviously limits the value of our conclusions. However, the size of our population is comparable with previously published series and our patients were selected on the basis of high suspicion of infection and underwent thorough workup. Another drawback of this study is failure to include a control group with no device infection. Nevertheless, other studies with control populations have shown no abnormal uptake. Finally, as in all studies on this topic, the lack of a gold standard for diagnosis of CIED infection is a limiting factor for evaluating a new diagnostic method.

### Conclusion

This study in patients implanted with CIED confirms high sensitivity and specificity of FDG PET/CT for diagnosis of skin and pocket infection but indicates lower accuracy for diagnosis of IE. The reliability of FDG PET/CT findings in management decision making varies according to the type of CIED infection.

### Conflict of interest: none declared.

### References


