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Early diagnosis of cardiac implantable electronic device generator pocket infection using ^{18}F-FDG-PET/CT

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Aims To examine the utility of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in the early diagnosis of cardiac implantable electronic device (CIED) generator pocket infection.

Methods and results A total of 86 patients with CIEDs were evaluated with ^{18}F-FDG PET/CT imaging: 46 with suspected generator pocket infection and 40 without any history of infection. ^{18}F-FDG activity in the region of the generator pocket was expressed as a semi-quantitative ratio (SQR)—defined as the maximum count rate around the CIED divided by the mean count rate between normal right and left lung parenchyma. All patients underwent standard clinical management, independent of the PET/CT result. Patients with suspected generator pocket infection that required CIED extraction ($n = 32$) had significantly higher ^{18}F-FDG activity compared with those that did not ($n = 14$), and compared with controls ($n = 40$) [SQR: 4.80 (3.18–7.05) vs. 1.40 (0.88–1.73) vs. 1.10 (0.98–1.40), respectively; $P < 0.001$]. On receiver operator characteristic analysis, SQR had a high diagnostic accuracy (area under curve = 0.98) for the early identification of patients with confirmed infection (i.e. those ultimately needing extraction)—with an optimal SQR cut-off value of >2.0 (sensitivity = 97%; specificity = 98%).

Conclusion This study highlights the potential benefits of evaluating patients with suspected CIED generator pocket infection using ^{18}F-FDG PET/CT. In this study, ^{18}F-FDG PET/CT had a high diagnostic accuracy in the early diagnosis of CIED generator pocket infection, even where initial clinical signs were underwhelming.

Keywords Pacemakers • Infection • Generator pocket infection • Imaging and diagnostics • Nuclear cardiology • ^{18}F-FDG PET/CT

Introduction

Expanding clinical indications have resulted in increasing numbers of patients being treated with a cardiac implantable electronic device (CIED). Despite improved surgical techniques and the use of prophylactic antimicrobial therapy, the number of CIED infections is increasing disproportionately to the rate of implantation, and this represents a major healthcare challenge.[1,2] Between 2004 and 2006, there was a 57% increase in the rate of hospitalizations for CIED infection.[1]

CIED infections may be categorized into those that are associated with endocarditis (CIED-IE) or lead infections (CIED-LI), and those

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that are confined to the generator pocket (CIED-GPI). Patients with CIED-IE/LI typically present with signs of systemic illness and usually have abnormal blood markers for infection.[3] Approximately 70% of patients with CIED infection present with overt infective signs in the region of the generator pocket (impending or completed device exteriorization, abscess formation, and purulent discharge), and in these patients, the need for extraction without additional investigation is well established.[4,5] However, the clinical presentation of CIED-GPI is highly variable and patients may also present with only mild localized signs (pain, with or without subtle erythema) posing a diagnostic challenge as these symptoms can be attributed to both infective and non-infective causes. Nevertheless, delays in diagnosing and treating generator pocket infection can result in progression to CIED-IE/LI or severe sepsis, and therefore worse clinical outcomes.[5,6] Accordingly, a non-invasive test with sufficient sensitivity and specificity to confirm or exclude infection in cases with a low or intermediate pre-test probability of infection at initial presentation would be desirable.

^{18}F-Fluorodeoxyglucose positron emission tomography with combined computed tomography (^{18}F-FDG PET/CT) has been used in the investigation of malignancy for over a decade. More recently, it has been utilized as a diagnostic tool in infection. Early studies into the utility of ^{18}F-FDG for CIED infection have been mostly limited to the evaluation of individuals known to have 'confirmed' or high probability of CIED infection, i.e. subject to spectrum bias. Data are particularly lacking for the utility of ^{18}F-FDG PET/CT to evaluate patients with mild symptoms and signs that are confined to the generator pocket. Accordingly, we sought to examine the utility of ^{18}F-FDG PET/CT in the early diagnosis of CIED-GPI across all pre-test probability groups.

Methods

Design and subjects

A prospective observational study of consecutive patients aged 18 and over referred to the Manchester Heart Centre with suspected CIED-GPI between December 2012 and May 2014 who underwent ^{18}F-FDG PET/CT examination. The control group comprised patients with chronically implanted CIED undergoing ^{18}F-FDG PET/CT for malignancy surveillance, but without clinical evidence of generator pocket or systemic infection. Patients satisfying Duke criteria for possible or definite CIED-IE/LI or those with echocardiographic evidence of CIED-IE/LI were excluded. All patients gave informed consent for ^{18}F-FDG PET/CT assessments and the institutional review board approved the study protocol.

Clinical assessment

All suspected CIED-GPI cases were reviewed and examined by an experienced consultant cardiologist specializing in device extraction (A.M.Z., >10 years experience). Baseline evaluation included (i) clinical assessment for signs and symptoms of CIED infection; (ii) grading of erythema in the region of the generator pocket according to a Clinical Erythema Assessment (CEA) Scale[7] [0 = clear of erythema, 1 = almost clear of erythema (slight redness), 2 = mild erythema (definite redness), 3 = moderate erythema (marked redness), 4 = severe erythema (fiery redness); (iii) blood markers of infection, including three sets of blood cultures, full blood count and C-reactive protein (CRP); and (iv) standard transthoracic echocardiography performed in accordance with ESC/EACVI guidelines.[8] Where possible, the blood cultures were obtained before antimicrobial therapy was commenced.

Possible vs. definite CIED-GPI

Patients were divided into 'possible' or 'definite' CIED-GPI groups according to specific clinical criteria. 'Possible' CIED-GPI (Group 1) was defined as localized pain in the region of the generator pocket with or without slight (CEA grade 1) erythema of the overlying skin. 'Definite' CIED-GPI (Group 2) was defined as significant erythema (CEA grade 2 or above) in the region of the generator pocket, abscess formation, purulent discharge or wound dehiscence or erosion; with or without positive blood cultures, but without evidence of lead or endocardial involvement, according to published guidelines.[9–11]

^{18}F-FDG PET/CT scanning was performed in all cases and controls according to the same protocol. *Figure 1* illustrates the study protocol. All patients with 'definite' infection underwent extraction; in patients with 'possible' infection the decision to undergo extraction or not was made after further clinical review by the same cardiologist (A.M.Z., >10 years experience in CIED management) on the basis of persistence or progression of the symptoms and/or signs. Although there was no formal blinding from the PET/CT results, the cardiologist was instructed to manage patients as per their usual clinical practice. For those patients undergoing device extraction, samples were sent for microbiological analysis.

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

All subjects were fasted for 4–6 h prior to the scan. A blood glucose of 3.5–12 mmol/L at the time of study was achieved. ^{18}F-FDG PET/CT imaging was performed using a Siemens Biograph mCT (Siemens Healthcare) with an extended axial field of view (TrueV). A low-dose CT scan was obtained for attenuation correction (AC) of the PET images, which were acquired in 3D mode at 2.5 min per bed position between 60 and 90 min post-injection of 350–400 MBq ^{18}F-FDG.

^{18}F-FDG PET/CT image analysis

Images were viewed using Volumetrix software on a GE Xeleris workstation (GE Healthcare). All images were analysed by an experienced nuclear medicine physician (J.J., 25 years experience) and a medical physicist. Where there was disagreement arbitration was sought from a third observer (G.A.B., nuclear medicine physician, 14 years experience). A positive scan was defined by increased FDG activity on the AC PET images around the device, i.e. maximal standardized uptake value (SUV_{max}) greater than mediastinal blood pool activity. A negative scan was defined as no increased FDG activity around the device relative to surrounding tissues or mediastinal blood pool. However, definition of a metric derived from the PET images to quantify the presence and extent of infection is challenging. In PET CT imaging, streak artefacts on the CT images from metal implants have the potential to propagate to the CT-based AC maps causing inaccuracies in the quantification of tissue tracer uptake in the AC PET images. This is of concern when trying to quantify uptake of ^{18}F-FDG around a metallic CIED from AC PET images. Therefore, Sarrazin *et al.* defined a semi-quantitative ratio (SQR) derived from count rates in the non-AC PET images[12] to circumvent any errors in tracer uptake introduced during the AC process. The SQR is defined as the maximum count rate in the region surrounding the CIED (and associated leads) to the mean count rate between normal left and right lung parenchyma. Areas of abnormal lung parenchyma were avoided in the analysis.

Surgical technique and collection of microbiological samples

Where the CIED system was extracted the operative technique for collection of samples was standardized and performed by a highly experienced cardiologist specializing in CIED extraction (A.Z., >10 years experience). Upon opening the pocket any pus was aspirated using a

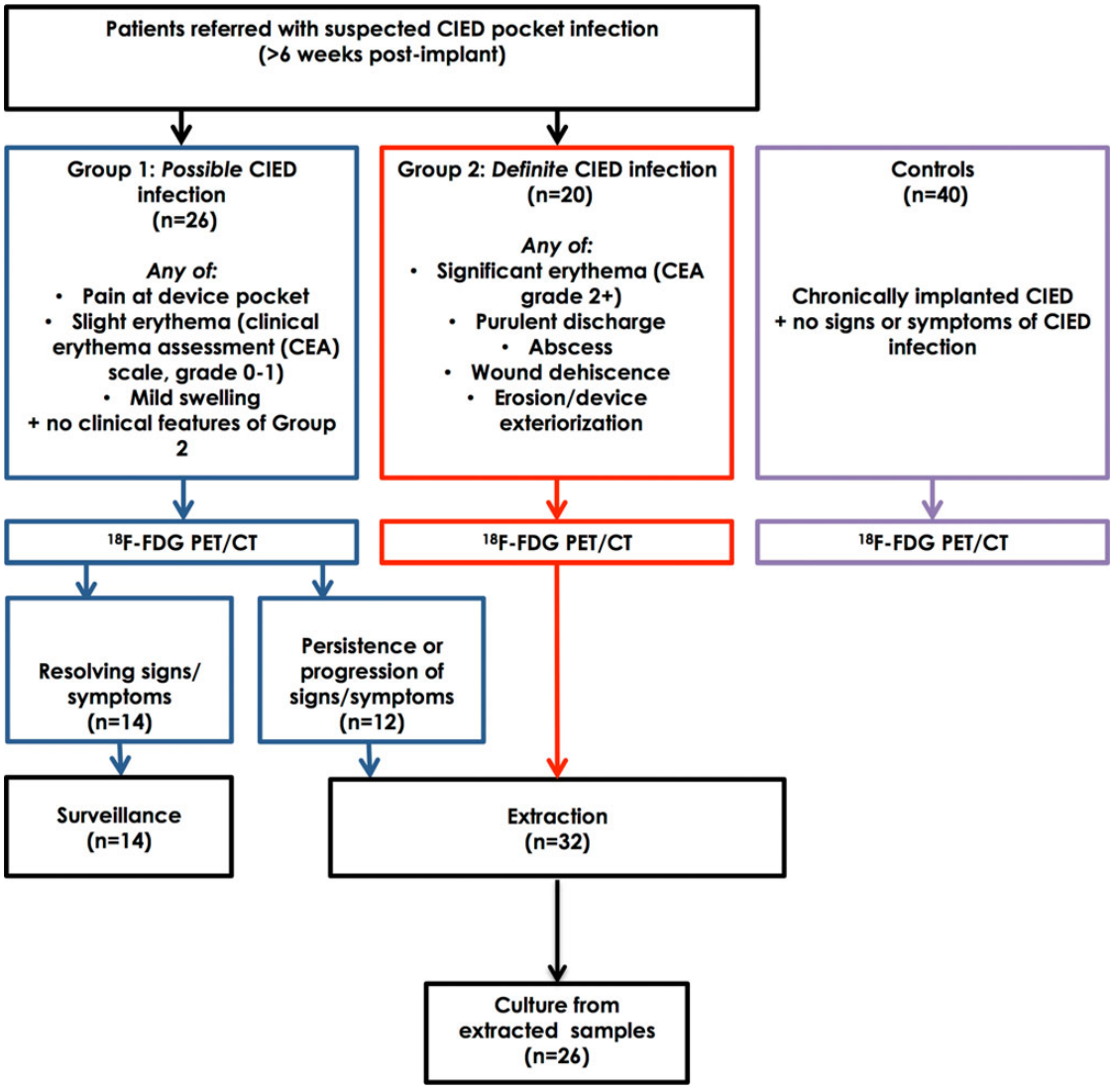

Figure 1 Clinical protocol for assessment and management of patients with suspected CIED generator pocket infection.

sterile syringe; 1–3 mL of pus was injected into a paediatric FAN blood culture bottle (Biomerieux, UK) and a further charcoal swab was obtained. Where there was no fluid or pus present, sterile saline was introduced into the pocket following removal of the pulse generator and the washings were sent for microbial analysis. Samples of superficial tissue from the pocket (at the incision site) and deep tissue (from the floor of the pocket) were obtained and sent for microbial analysis. Finally, extravascular portions of the lead were cut and sent for microbial analysis before the intravascular portion of the lead was extracted. All leads were extracted transvenously via the subclavian or femoral routes. Lead tips were also sent for analysis. Each organism isolated was reported to species level with appropriate sensitivity results. Direct sensitivity testing was performed using the British Society for Antimicrobial Chemotherapy (BSAC) standards.[13]

Statistical analysis

Statistical analyses were performed using R version 2.15.2. (libraries psych, epiR, and epicalc).[14–17] Data are presented as median (IQR) or *N* (%) as appropriate. Group medians were compared a Mann–Whitney U-test or Kruskall–Wallis test (multiple groups) as appropriate. Categorical data were compared using Fisher's exact test. Receiver operating characteristic (ROC) analysis was performed to determine the diagnostic accuracy of SQR to detect (i) possible or definite infection (as per pre-test clinical criteria), (ii) definite infection (as per pre-test clinical criteria), and (iii) the clinical need for extraction, i.e. confirmed CIED-GPI (using eventual clinical course as the reference standard). Optimal SQR thresholds from the ROC curve were determined using the maximum Youden index (J = sensitivity + specificity − 1). All tests were two-tailed and $P < 0.05$ was considered statistically significant.

Results

Study population

In total, 86 patients with CIEDs were evaluated with ^{18}F-FDG PET/CT imaging: 46 with suspected CIED-GPI and 40 controls without any history of infection. Further demographic information and clinical presentation are presented in *Tables 1* and *2*, respectively.

Table 1 Demographics of study participants

	Group 1: 'Possible' infection ($n = 26$)	Group 2: 'Definite' infection ($n = 20$)	*P*
Male sex, *n* (%)	18 (69)	15 (75)	0.408
Median age, years (IQR)	61.0 (52–80)	65.6 (57–80)	0.176
Device Type			
PPM, *n* (%)	17 (65)	8 (40)	0.136
ICD/CRT-D, *n* (%)	9 (35)	12 (60)	0.136
Co-morbidities			
Median age-adjusted Charlson index (IQR)	2 (0–3)	4 (2–5)	0.136
Adult congenital heart disease, *n* (%)	3 (12)	2 (10)	1.000
Diabetes, *n* (%)	3 (12)	3 (15)	1.000
Chronic kidney disease stage ≥3, *n* (%)	3 (12)	3 (15)	1.000

PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; CRT-D, cardiac resynchronization therapy-defibrillator.

Table 2 Clinical presentation and laboratory markers for infection in patients with suspected CIED infection

	Group 1 ($n = 26$)	Group 2 ($n = 20$)	*P*
Presentation			
Fever, *n* (%)	1 (4)	3 (15)	0.303
Device erosion, *n* (%)	0 (0)	5 (25)	0.011
Abscess, *n* (%)	0 (0)	6 (30)	0.004
Purulent discharge, *n* (%)	0 (0)	2 (10)	0.184
Mild swelling, *n* (%)	1 (4)	0 (0)	0.467
Localized pain, *n* (%)	24 (92)	6 (30)	<0.0001
Erythema[a], *n* (%)	6 (23)	7 (35)	0.748
Grade 1	6	0	0.029
Grade 2	0	2	0.1836
Grade 3	0	3	0.075
Grade 4	0	2	0.184
Blood markers of infection			
Median WCC (IQR)	7.5 (6.6–8.3)	7.2 (6.2–9.1)	0.407
Elevated WCC, *n* (%)	2 (8)	2 (10)	1.000
Median CRP (IQR)	2.0 (1.5–11.0)	2.0 (2.0–5.5)	0.084
Elevated CRP, *n* (%)	5 (19)	4 (20)	1.000
Positive blood cultures, *n* (%)	0 (0)	1 (5)	0.435
Device-related factors			
Median time (days) from last procedure to presentation (IQR)	309 (121–1245)	1385 (128–2667)	0.113
Generator replacement or revision within 12 months, *n* (%)	6 (23)	4 (20)	1.000
Site revision within 12 months, *n* (%)	1 (4)	2 (10)	0.572
Median length (days) of in-patient stay (IQR)	0 (0–2)	18 (8–29)	<0.0001
Median length in-patient stay (days) for infected cases (IQR)	5 (1–17)	18 (8–29)	0.036
Pre-treatment with antimicrobials before PET/CT (receiving antibiotics at time of PET/CT examination)	8 (31)	18 (90)	0.0002
Median duration of antimicrobial therapy (days) before PET/CT examination (IQR)	0 (0–8)	14 (7–14)	0.0001

WCC, white cell count; CRP, C-reactive protein.
[a]Clinical Erythema Assessment Scale.

Clinical outcome

Of the 46 patients with suspected CIED-GPI, 26 were categorized as 'possible' infection (Group 1) and 20 as 'definite' infection (Group 2) based on the specified clinical criteria.

Group 1

Of the 26 patients in Group 1 ('possible' infection), 12 were ultimately considered to have CIED-GPI based on their clinical progression which led to CIED extraction. An additional patient, originally considered as a 'possible' case of CIED-GPI, did not undergo extraction because the symptoms in the region of the pocket had completely resolved at subsequent clinical review—this patient also had a positive PET/CT result (SQR 2.6). The latter was considered to be a 'false positive' given clinical resolution with conservative management but the possibility of a self-limiting infection remains. A follow-up ^{18}F-FDG PET/CT assessment in this individual performed 3 months later for evaluation of a suspicious left upper lobe lung lesion identified on the original scan, subsequently demonstrated a reduction in SQR (1.7) in the region of the CIED generator pocket. We continue to closely monitor this individual for signs of infection.

The remaining 13 patients in Group 1 remained well during clinical follow-up [237 (129–384) days] with no crossover to extraction and were all found to have a normal ^{18}F-FDG PET/CT result.

Group 2

All 20 (100%) patients in Group 2 ('definite' infection) underwent system extraction as planned. Seventeen of these patients were found to have a positive ^{18}F-FDG PET/CT result (see Supplementary data online).

Localized erythema

While the intensity of erythema in the region of the generator pocket between the two groups was visually distinct ($P = 0.029$, *Table 2*), ^{18}F-FDG uptake within the CIED pocket was increased in all 13 patients with erythema (grade 1–4) that we examined (*Table 3*). 11/13 (84.6%) cases had microbiological evidence of infection (Group 1, $n = 4$, Group 2, $n = 7$).

Localized pain only

Out of the 18 patients who presented with lone pain in the region of the generator pocket, 6 (33.3%) had abnormal ^{18}F-FDG PET/CT scans (*Figure 2*). A pathogen was recovered from three of these six

Table 3 Profile and infective status of individual patients in Group 1

Episode	Presentation	^{18}F-FDG result	SUV_{max}	SQR around CIED	Outcome
1	Grade 1 erythema and pain	Positive	2.1	2.4	Extracted
2	Grade 1 erythema and pain	Positive	7.1	6.7	Extracted
3	Grade 1 erythema and pain	Positive	4.9	8.3	Extracted
4	Grade 1 erythema and pain	Positive	7.8	6.4	Extracted
5	Grade 1 erythema	Positive	7.5	9.4	Extracted
6	Grade 1 erythema	Positive	4.9	6.6	Extracted
7	Pain	Positive	4.7	4.7	Extracted
8	Pain	Positive	4.9	4.5	Extracted
9	Pain	Positive	5.1	4.7	Extracted
10	Pain	Positive	3.4	3.0	Extracted
11	Pain	Positive	3.6	6.6	Extracted
12	Pain	Positive	2.8	3.2	Extracted
13	Pain and mild swelling. Signs completely resolved at re-review. Incidental LUL lesion on PET	Positive	2.5	2.6	Not extracted
14	Pain and fever	Negative	1	1.1	Not extracted
15	Pain	Negative	1.3	0.8	Not extracted
16	Pain (ACHD, multiple generator changes)	Negative	1.3	1.5	Not extracted
17	Pain	Negative	1.2	0.5	Not extracted
18	Pain	Negative	2.0	1.8	Not extracted
19	Pain (ACHD)	Negative	1.3	1.8	Not extracted
20	Pain (ACHD)	Negative	<1.0	0.7	Not extracted
21	Pain	Negative	1.4	1.8	Not extracted
22	Pain	Negative	1.4	1.3	Not extracted
23	Pain	Negative	1.1	1.2	Not extracted
24	Pain	Negative	1.2	0.6	Not extracted
25	Pain	Negative	1.3	1.1	Not extracted
26	Pain	Negative	1.5	1.5	Not extracted

ACHD, adult congenital heart disease; LUL, left upper lobe.

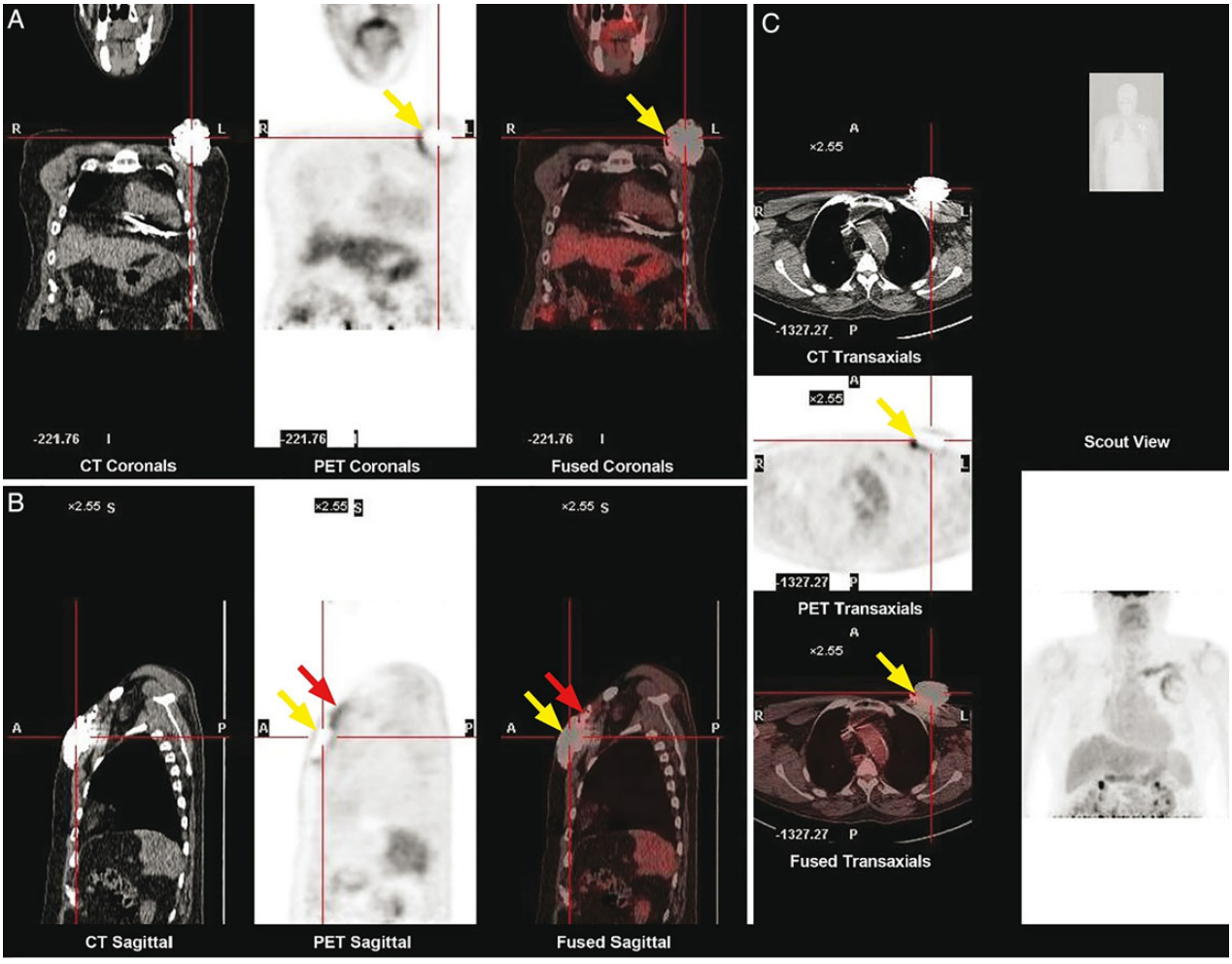

Figure 2 Example of a positive ^{18}F-FDG PET/CT scan in a Group 1 individual with pain at the generator pocket site. (*A*) Increased ^{18}F-FDG uptake is seen in the region of the left pre-pectoral pocket on the coronal views (yellow arrows). (*B*) In the sagittal plane, increased ^{18}F-FDG uptake can be seen on the muscular aspect of the pre-pectoral generator (yellow arrows) and along the proximal portion of the leads (red arrows). (*C*) Increased ^{18}F-FDG uptake visualized on the muscular aspect of the generator pocket (yellow arrows).

cases (50%). In contrast, the patients who presented similarly with localized pain but had negative ^{18}F-FDG PET/CT findings ($n = 12$) were managed successfully with a conservative strategy.

SUV_{max}

Increased ^{18}F-FDG uptake (SUV_{max}) in the region of the generator pocket was seen in 85% ($n = 17$) of Group 2 ('definite' infection) patients compared with 50% ($n = 13$) of Group 1 ('possible' infection) patients. No control cases showed increased ^{18}F-FDG uptake in the region of the generator pocket.

In those Group 1 patients without increased ^{18}F-FDG uptake in the region of the pocket ($n = 13$, 50%), there was also no increase anywhere along the visualized length of the leads (*Figure 3*).

SQR

Overall, SQR was significantly higher in those cases that required extraction ($n = 32$) compared with those that were successfully managed conservatively ($n = 14$), and compared with controls ($n = 40$) [SQR: 4.80 (3.18–7.05) vs. 1.40 (0.88–1.73) vs. 1.10 (0.98–1.40) respectively; $P < 0.001$] (*Figures 4 and 5*).

Amongst those initially assessed as only 'possible' infection, i.e. Group 1 ($n = 26$), the SQR was also significantly higher in those that ultimately required CIED extraction ($n = 12$) compared with those that did not ($n = 14$) [4.75 (4.18–6.62) vs. 1.40 (0.88–1.73); $P < 0.001$].

SQR thresholds

SQR had a high diagnostic accuracy to identify confirmed CIED-GPI (defined by eventual clinical need for extraction), and the optimal threshold was >2.0 [97% sensitivity (84–100%), specificity 98% (90–100%), area under the curve (AUC) = 0.98, $J = 0.95$].

The optimal threshold for differentiating suspected CIED-GPI ('possible' or 'definite' infection) from controls was a SQR >1.75 [sensitivity 76% (61–87%), specificity 100% (87–100%), AUC = 0.88, $J = 0.76$]; and the optimal threshold to differentiate only those categorized as 'definite' infection from the rest was

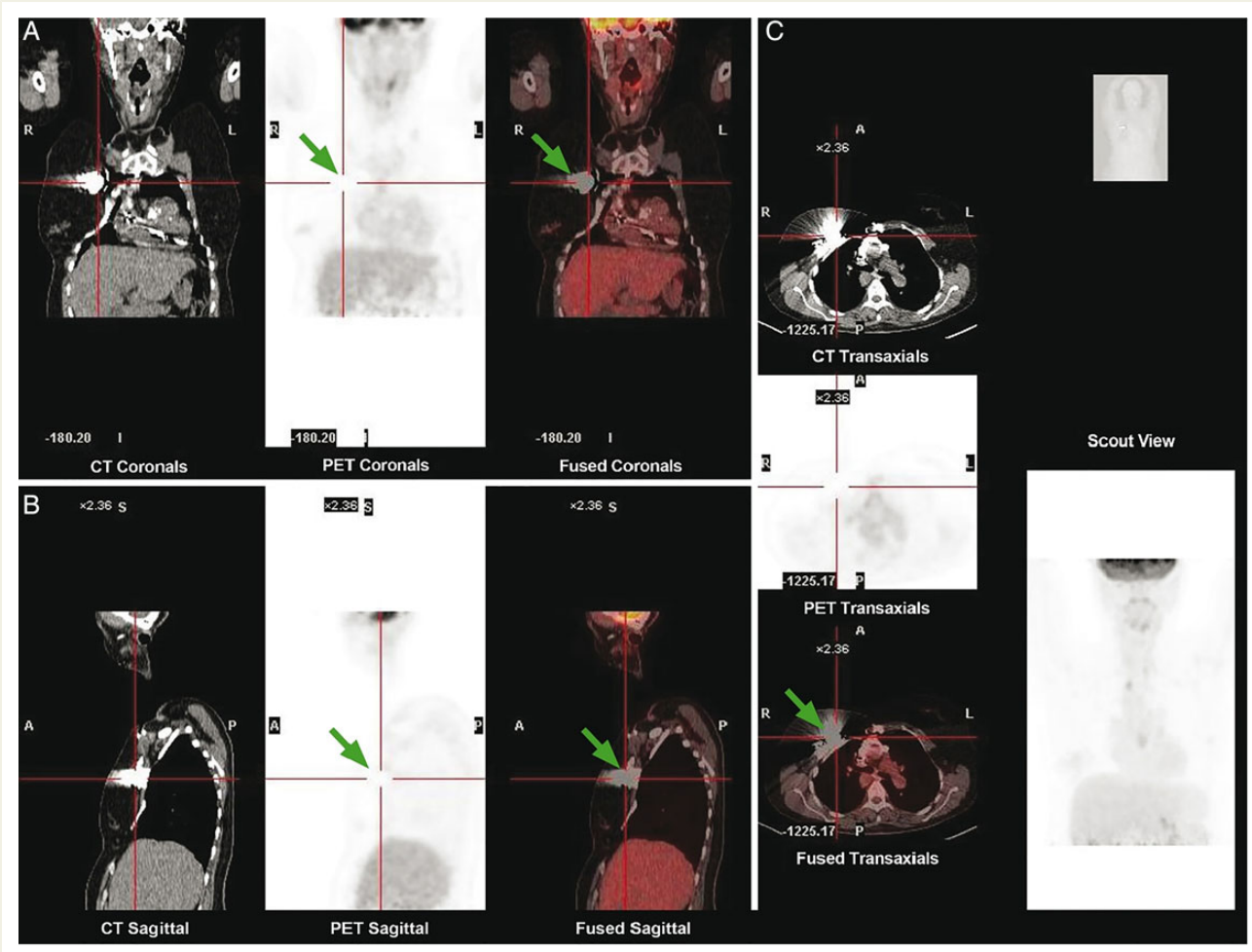

Figure 3 Example of a negative ^{18}F-FDG PET/CT scan in a Group 1 patient who presented with pain at the generator pocket site. This individual, with a history of grown up congenital heart disease and 20-year-old right-sided pacing leads (episode 16), presented with pain in the region of their right pre-pectoral pocket 4 years after generator box change. There is no evidence of increased ^{18}F-FDG uptake in the region of the right-sided generator pocket (green arrows) or along the proximal portion of the leads (*A*, *B* and *C*).

SQR $>$1.9 [sensitivity 95% (75–100%), specificity 80% (69–89%), AUC = 0.88, J = 0.75].

Microbiological analysis

Of the 32 cases (from both Groups 1 and 2) that underwent extraction, a pathogen was identified in 26 (81.3%) cases. Out of the 12 cases from Group 1 undergoing extraction, 7 had microbiological evidence of infection. In four cases, no pathogen was recovered from any of the samples analysed; in the remaining case a pathogen could not be sought due an error in specimen collection. In Group 2, microbiological evidence of infection was available for 19 out of 20 cases. In one individual, there was no growth from any of the recovered specimens.

Discussion

This study is the largest prospective evaluation of ^{18}F-FDG PET/CT for suspected CIED-GPI and examines its role across a full spectrum of presentations ranging from peri-pocket persistent pain to pocket abscess and device exteriorization. The two main findings are that (i) ^{18}F-FDG activity is significantly higher in patients who ultimately require CIED extraction compared with those who resolve with conservative treatment or compared with normal controls; and (ii) ^{18}F-FDG activity has a high diagnostic accuracy (AUC = 0.98) for the early identification of patients ultimately needing extraction, using an optimal SQR cut-off value of $>$2.0.

In this study, we have demonstrated the utility of ^{18}F-FDG PET/CT in the early diagnosis of CIED-GPI when the clinical diagnosis is unclear due to mild symptoms that could be attributed to either infective or non-infective causes. This is of particular clinical importance as pain, with or without subtle erythema, in the region of the generator pocket is a frequent complaint of patients seen in CIED follow-up clinics.[5] At present it is unclear what proportion of these patients have subclinical infection that will progress over time, resulting in more severe complications.

Sarrazin *et al.* have previously reported that ^{18}F-FDG PET/CT is useful in differentiating between individuals with CIED infection (not just pocket infection) and recent post-implant changes.[12]

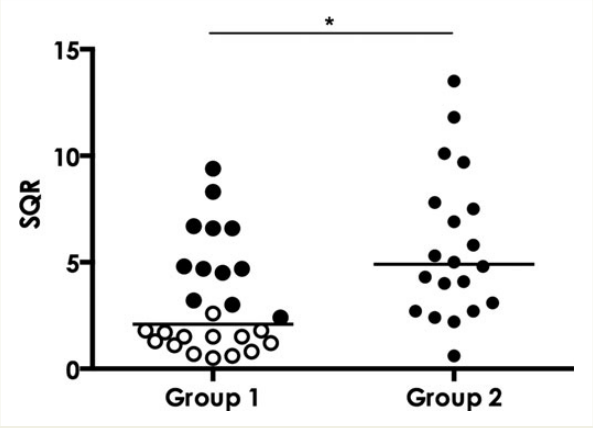

Figure 4 ^{18}F-FDG uptake in patients with suspected CIED generator pocket infection. Individuals in Group 1 ($n = 26$) and Group 2 ($n = 20$) underwent ^{18}F-FDG PET/CT assessment. ^{18}F-FDG uptake in the region of the generator pocket, as expressed by the SQR, was lower in Group 1 than Group 2 [SQR 2.10 (1.28–4.73) vs. 4.90 (2.80–7.73), $P = 0.003$]. Lines represent median values. Unfilled circles illustrate the patients whose clinical symptoms resolved and were managed conservatively ($n = 14$).

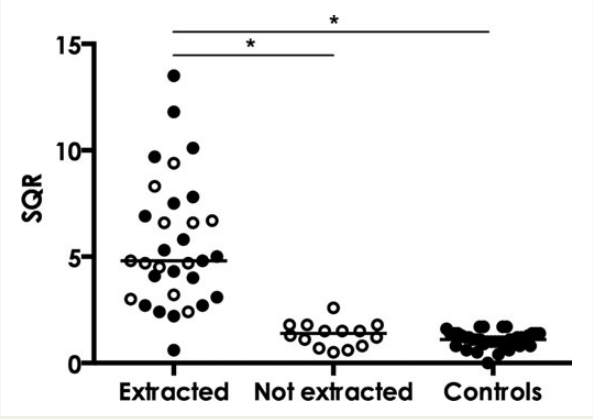

Figure 5 ^{18}F-FDG uptake in extracted cases, non-infected cases and controls. SQR was significantly greater in patients who underwent extraction ($n = 32$) than in non-infected cases ($n = 14$) and controls ($n = 40$) [SQR 4.80 (3.18–7.05) vs. 1.40 (0.88–1.73) vs. 1.10 (0.98–1.40) respectively; $P < 0.001$]. There was no significant difference in SQR between non-infected cases and controls. Unfilled circles illustrate subjects presenting with pre-test 'possible' infection (Group 1). Lines represent median values.

However, such previous studies have, for the most part, only examined individuals with known CIED-GPI or a high pre-test probability and are therefore limited by a spectrum bias.[12,18,19] Individuals with mild local symptoms and a lower pre-test probability of infection at presentation have not been examined. Therefore, by including patients with a pre-test clinical assessment of suspected but not proven 'possible' CIED-GPI ($n = 26$) as well as those with a pre-test clinical assessment of 'definite' CIED-GPI, the current study includes a full spectrum of risk and is more applicable to real-world practice.

In this study, FDG PET/CT imaging had a high diagnostic accuracy (AUC = 0.98) for the early identification of patients ultimately needing extraction, using an optimal SQR cut-off value of >2.0 (sensitivity 97%, specificity 98%). This may help guide a strategy of early extraction vs. futile conservative management—even in patients who initially present with only mild localized signs, or where the infective status is not immediately clinically obvious.

In this study, we also compared FDG PET/CT imaging to standard pre-test clinical assessment by an experienced cardiologist specializing in CIED management. The high diagnostic accuracy of FDG PET/CT to distinguish possible or definite pre-test probability CIED-GPI groups from controls (AUC = 0.88) or to distinguish the definite pre-test probability CIED-GPI group from all other groups (AUC = 0.88) open up the possibility of FDG PET/CT imaging being used where a specialist opinion and clinical assessment is not immediately available—as a means of stratifying 'definite' cases for prompt referral to specialist centres for early extraction. Prompt diagnosis of non-valvular CIED infections is of paramount clinical importance as failure to do so can delay extraction and result in endovascular spread of infection or endocarditis associated with significant morbidity and mortality.[11,20,21] Early and complete CIED removal, on the other hand, is associated with improved 30 day and 1 year outcomes.[20] Despite this, delays in CIED extraction in favour of surveillance and a trial of antimicrobial therapy are not uncommon practice.

Our results also offer insight into the relative importance of subtle signs such as localized erythema and lone pain. We suggest that the presence of erythema (of any grade) in patients with suspected CIED-GPI should be considered a red-flag clinical sign. On the other hand, in our study, 12 the patients who presented with only localized pain had negative ^{18}F-FDG PET/CT findings ($n = 12$) and were successfully managed with a conservative strategy. Therefore, localized pain alone may more commonly relate to non-infective pathology, such as superficial placement of the device in the absence of infection and a negative ^{18}F-FDG PET/CT could be used to offer reassurance in this group.

In summary, optimal decision-making in patients with suspected CIED-GPI requires an assessment of the probability of infection. We believe our results show that an imaging-based approach would be helpful in patients with low and intermediate probability of CIED-GPI when there are subtle clinical signs and normal blood markers for infection.

Correct identification of microbial pathogens is essential for the targeted treatment of CIED infections. Nevertheless, microbiological confirmation of infection is not a pre-requisite for the diagnosis of CIED-GPI,[9,11] because the diagnosis is based on clinical criteria. Culture-negative cases of CIED pocket infections are well recognized and have been reported to occur in up to 16% of patients.[22] Therefore, negative culture results cannot be used to rule out a diagnosis of infection. There were five cases of culture-negative CIED pocket infection in our series (Group 1, $n = 4$; Group 2, $n = 1$, *Table 4*). Three of these cases were pre-treated with antimicrobials prior to CIED extraction (Group 1, $n = 2$; Group 2, $n = 1$). Reasons for negative cultures include empirical antimicrobial therapy prior to culture

Table 4 Pathogens identified from the extracted samples

Pathogen	Group 1 ($n = 11^a$)	Group 2 ($n = 20$)
Monomicrobial, *n* (%)	7 (63)	12 (60)
Polymicrobial, *n* (%)	0 (0)	7 (35)
No growth, *n* (%)	4 (36)	1 (5)
Organism causing CIED infection		
Staphylococcus aureus sp., *n* (%)	0 (0)	3 (15)
CNS, *n* (%) [polymicrobial]	6 (55)	14 (70) [5]
Enterococcus sp., *n* (%)	1 (9)	1 (5)
Other, *n* (%) [polymicrobial]	0 (0)	1 (5) [1]

CNS, coagulase negative staphylococci.
[a]Sampling error in one patient, no samples sent for that case.

of extracted samples, inappropriate culture techniques, and difficult to culture or non-culturable pathogens.

Limitations

The current study has some key limitations. First, the use of antibiotics prior to PET/CT examination and extraction in 26 patients may have impacted on both ^{18}F-FDG uptake and recovery of pathogens from extracted samples. Antibiotic therapy has been shown to cause a significant decrease in ^{18}F-FDG uptake in other conditions.[23] However, this puts our results into real-world context as it is common practice for antibiotics to be given by primary care givers and emergency departments on first contact. In the current study, three Group 2 patients ('definite' infection at initial presentation) had no increased ^{18}F-FDG activity in the region of the device pocket [maximal standardized uptake value (SUV_{max}) less than mediastinal blood pool activity]. Two of these were managed with prolonged courses of antibiotics before onward referral to our centre for extraction. While two of the three patients had an SQR >1.75, one patient (draining sinus, prolonged antibiotic treatment) had an SQR of 0.6. This case was considered a 'false negative'. It is postulated that chronic antimicrobial therapy was a significant contributing factor to the negative PET/CT result in this case. All remaining patients who underwent extraction and received prior treatment with antimicrobials ($n = 24$) had increased ^{18}F-FDG uptake in the region of the device pocket (SQR >2.0).

Although the majority of subjects were referred to our centre from other hospitals, PET/CT examinations and extraction procedures were all performed at a single centre. This was an observational study. PET/CT was not used to guide the decision to extract or otherwise. The decision to proceed with extraction was made on standard clinical criteria, i.e. the persistence and/or progression of clinical symptoms and signs of infection. This decision was made by the same cardiologist in all cases. Although the clinician was not formally blinded to the FDG PET/CT results, they were instructed to act as per their usual clinical practice and without bias from imaging findings. Despite best intentions, we concede it is possible that knowledge of the FDG PET/CT result (positive or negative, but not the SUV_{max} or SQR) may have influenced clinical decisions. In particular, a negative FDG PET may have potentially re-inforced the decision to adopt a conservative strategy in those Group 1 individuals whose clinical symptoms and signs were not debilitating or did not progress with time. However, as testament to the cardiologist's intended lack of bias we highlight that there was one case with a positive scan (Group 1) who was managed conservatively due to resolution of clinical signs. Our data require validation in larger populations involving several hundred patients as part of a multi-centre study. Finally, the utility of PET/CT as a diagnostic tool in cases of CIED infection remains under investigation. Routine use of PET/CT outside research studies is not currently recommended.[9]

Conclusion

This study highlights the potential benefits of evaluating patients with suspected CIED-GPI using ^{18}F-FDG PET/CT. In this study, ^{18}F-FDG PET/CT had a high diagnostic accuracy in the early diagnosis of CIED-GPI—even where initial clinical signs were underwhelming. This represents a major step forward in our understanding of the potential applications of molecular imaging in CIED recipients.

Supplementary data

Supplementary data are available at *European Heart Journal—Cardiovascular Imaging* online.

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