Contribution of PET Imaging to the Diagnosis of Septic Embolism in Patients With Pacing Lead Endocarditis

Sana Amraoui, MD,a Ghoufrane Tlili, MD,b Manav Sohal, MBBS,c Benjamin Berte, MD,a Elif Hindié, MD, PhDb, Philippe Ritter, MD,a Sylvain Ploux, MD, PhDb, Arnaud Denis, MD,a Nicolas Derval, MD,a Christopher A. Rinaldi, MD, PhD,c Charles Cazanave, MD,d Pierre Jais, MD, PhD,a Michel Haissaguerre, MD, PhD,a Laurence Bordenave, MD, PhDb, Pierre Bordachar, MD, PhDb

ABSTRACT

OBJECTIVES The aim of this study was to investigate the role of 18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scanning in identifying septic embolism in patients with lead endocarditis.

BACKGROUND Lead endocarditis may be associated with septic embolism, in which case the administration mode, type, and duration of antibiotic therapy must be adapted. However, diagnosis can be challenging: magnetic resonance imaging (MRI) cannot be performed in the vast majority of patients with cardiac implantable electronic devices (CIEDs). FDG PET/CT scanning has been proposed as a diagnostic tool for suspected CIED infection.

METHODS Thirty-five consecutive patients with lead endocarditis were prospectively studied. FDG PET/CT scanning was performed and analyzed blindly by experienced nuclear medicine physicians to assess for the presence of septic embolism 2 days before lead extraction.

RESULTS FDG PET/CT scanning identified septic emboli in 10 patients (29%): 7 with spondylodiscitis, 2 with septic pulmonary emboli, and 1 with an infected vascular prosthesis. Among the 7 patients with occult spondylodiscitis, 4 were asymptomatic, and 3 had back pain with negative CT imaging, MRI being contraindicated due to non-MRI-compatible CIEDs. Antimicrobial therapy was adapted (double antibiotic therapy with good bone penetration) and prolonged. Among other important ancillary findings, 3 patients presented focal FDG uptake in the colon (1 adenocarcinoma, and 2 resected polyps) and 2 in the esophagus (both cases confirmed as neoplasia).

CONCLUSIONS This study emphasizes the potential utility of FDG PET/CT scanning as a diagnostic tool for septic emboli in patients with pacing lead endocarditis. This promising diagnostic tool may be integrated in the diagnostic algorithm of patients with lead endocarditis because diagnosis of septic embolisms has a direct and significant impact on the therapeutic care pathway. (J Am Coll Cardiol Img 2016;9:283–90) © 2016 by the American College of Cardiology Foundation.
performed in the vast majority of patients with a cardiac implantable electronic device. The risk of septic embolism associated with lead endocarditis is therefore probably underestimated because septic emboli are not systematically sought in many cases despite possible important clinical implications. In patients with associated spondylodiscitis, the type, administration mode, and duration of antibiotic therapy must be adapted with a need for good penetration into the septic tissues (7).

18-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scanning has been recently proposed as a diagnostic tool for suspicion of lead endocarditis (8-13). Fused PET/CT imaging allows the metabolic information from PET to be combined with the high spatial resolution and anatomic information of CT. FDG PET/CT scanning has shown promise as a method for locating sites of occult infection (14).

In the present study, we sought to investigate the role of FDG PET/CT scanning in identifying septic embolism in consecutive patients with lead endocarditis.

METHODS

STUDY DESIGN. Thirty-five patients with a diagnosis of lead endocarditis were prospectively included in this institutional-approved single-center study. They were referred to our center for lead extraction. An FDG PET/CT scan was performed in each patient 48 h before lead extraction to assess for the presence of septic emboli. All patients included in the present study provided written informed consent.

DIAGNOSIS OF LEAD ENDOCARDITIS. The diagnosis of lead endocarditis was made according to the modified Duke criteria (15). All patients underwent a standardized clinical care pathway at our center. This included a detailed history, clinical examination, and routine blood tests including inflammatory markers, wound swabs, and multiple blood cultures (minimum of 3 sets). All patients had both transthoracic and transesophageal echocardiography performed (16,17). Images were reviewed independently by 2 specialists, with vegetations defined as an oscillating intracardiac mass on the leads, cardiac valve leaflets, or endocardial surface. The diagnosis was confirmed by lead culture after the extraction procedure.

ANTIBIOTIC THERAPY. All patients were treated with antibiotics before extraction of the entire infected device. Antibiotics were commenced when the diagnosis of lead endocarditis was made. Most of the patients were referred to our center for lead endocarditis treatment; consequently, the antibiotic therapy was started before hospitalization in our department and thus before FDG PET/CT scanning. The antibiotic regimen was adjusted according to microbiology results and was guided by an infectious disease specialist. Vancomycin was used as first-line empirical therapy until the culprit pathogen was identified. In accordance with the American Heart Association (AHA) consensus statement (18), antibiotics were administered for 2 to 4 weeks in cases of local infection and for 4 to 6 weeks in the presence of vegetation or septic embolism. In the particular case of spondylodiscitis, dual antibiotic therapy with bone penetration was administered for between 10 to 14 weeks, including 4 to 6 weeks intravenously, followed by 6 to 8 weeks orally (7,19,20).

FDG PET/CT SCANNING. In all patients, FDG PET/CT scanning was performed 48 h before extraction of the entire device. Patients with lead endocarditis underwent total-body PET/CT scanning (Discovery ST, General Electric Healthcare, Fairfield, Connecticut) after injection of 3 MBq/kg of $^{18}$F-FDG intravenously after an 8-h fasting period. Patients did not have a specific high-fat and low-carbohydrate diet. PET/CT imaging was performed 1 h after FDG injection. A low-dose noncontrast CT was obtained for attenuation correction and anatomic localization. The acquisition parameters were as follows: 140 kV, 80 mAs, slice thickness of 3.75 mm, pitch 1, with reconstruction interval, 1.75 mm. PET data were acquired in 3-dimensional mode at 3 min per bed position. Glucose levels were <8 mmol/l. An experienced reporter who was blind to the clinical data analyzed the PET/CT images. The analysis began with visualization of maximum intensity projection to look for pathological foci. Corrected attenuation images were used to locate the position of the hypermetabolic foci (21). Noncorrected images were also reviewed to enhance sensitivity and avoid errors in interpretation, especially around areas of high attenuation, as previously described (8). FDG-avid foci in the spine corresponding to intervertebral discs and/or adjacent vertebrae, with or without underlying CT abnormalities, were considered suspicious for spondylodiscitis given the clinical setting.

EXTRACTION OF INFECTED PACING SYSTEM. All extraction procedures were performed in an operating room by a cardiologist. In all patients, the leads were extracted via a transvenous approach with the patient under general anesthesia (22). When possible, extraction was performed initially from a superior approach using a combination of simple traction or laser sheath (CVX-300 Excimer laser system;
Spectranetics, Colorado Springs, Colorado) as required. When a superior approach failed or was not possible, extraction was performed from a femoral approach using a dedicated femoral workstation (Cook Vascular Inc., Vandergrift, Pennsylvania) using a needle’s eye or gooseneck snare as appropriate. All infected tissue and intravascular lead segments were separately sent for culture.

**STATISTICAL ANALYSIS.** Data are expressed as mean ± SD or median with quartiles when noted. Data were analyzed with the SPSS software package version 17.0 (SPSS Inc., Chicago, Illinois). In patients with and without septic embolism, the Mann-Whitney U test was performed to test for statistical differences in continuous parameters. A Fisher exact test was used appropriately to compare these 2 groups on nominal data. A value of p < 0.05 was considered statistically significant.

**RESULTS**

Table 1 shows the baseline characteristics for the 35 consecutive patients with lead endocarditis enrolled in this study.

**DIAGNOSIS OF SEPTIC EMBOLISMS IN PATIENTS WITH LEAD ENDOCARDITIS. Septic embolisms.** FDG PET/CT scanning identified septic emboli in 10 of 35 patients (29%): 7 spondylodiscitis, 2 septic pulmonary emboli, and 1 infected aortobifemoral vascular prosthesis (Table 2), confirmed by clinical follow-up. Table 3 shows the clinical characteristics of patients with and without septic emboli. There were no differences between the 2 groups, except increased C-reactive protein levels.

Among the 7 patients with spondylodiscitis, 4 were totally asymptomatic: they did not present with clinical vertebral signs, and this diagnosis was only made after visualization of hotspots along the vertebral column. In 1 of these asymptomatic patients, FDG PET/CT scanning identified a diffuse spondylodiscitis in C5/C6/C7, T4/T5, and T6/T7 (Figure 1). The 3 remaining patients were symptomatic and presented with dorsal pain. However, the diagnosis could not be confirmed with other imaging tools (plain radiography and CT scanning) and MRI could not be performed in any of these patients. The diagnosis of spondylodiscitis had a direct therapeutic impact: antimicrobial therapy was prolonged to a total duration of 12 weeks, including a longer intravenous infusion (4 weeks), with choice of antibiotics demonstrating high bone penetration. To avoid spinal cord compression, there was a need for rachis immobilization. No patient underwent vertebral surgery. All patients were assessed by a rheumatologist with special attention to neurological signs of spinal cord compression.

One patient was found to have a septic embolism in the proximal extremity of his aortobifemoral prosthesis (Figure 2). In this patient, FDG PET/CT scanning also detected a large esophageal neoplasm with extension into the superior mediastinum. Palliative treatment was started and the 53-year-old patient died rapidly.

**Other findings.** Three patients presented with FDG uptake localized to the colon, 1 patient with a large mass in the mediastinum (esophageal neoplasm described above), and 1 with a mass in the inferior third of the esophagus: further investigations confirmed the suspicion of neoplasia and chemotherapy was started at an early stage, before clinical manifestations. Colonoscopy was performed in the 3 patients with focal colonic uptake. In 1 patient, an adenocarcinoma was diagnosed and an adapted treatment pathway was started (surgery and chemotherapy). Benign polyps were resected from the remaining 2 patients.

**FDG PET/CT SCANNING SENSITIVITY PERFORMANCE FOR LEAD ENDOCARDITIS.** This FDG PET/CT imaging examination was performed while patients were...
receiving antibiotic therapy in 77% of cases. There was FDG uptake along the lead in 19 of 35 (54%) patients. Among the false negative results, 14 of 16 (88%) patients were treated with antibiotics before FDG PET/CT scanning. Among the true positive results, 13 of 19 (68%) patients were receiving antibiotic therapy ($p = 0.24$).

**DISCUSSION**

Lead endocarditis is associated with important morbidity due to systemic infection. In fact, with the associated hypermobile vegetations, the infection is not only limited to the lead. Thus, septic embolism must be considered when a diagnosis of lead endocarditis is made to adapt the therapeutic pathway. However, the diagnosis may be difficult because MRI cannot be performed in most cases. In this study, we sought to investigate the role of FDG PET/CT scanning in identifying septic emboli in patients with lead endocarditis.

Our main findings were:
1. Septic emboli were found in 29% of patients with lead endocarditis, with FDG PET/CT scanning.
2. Spondylodiscitis was identified in 20% of patients. In 4 cases the emboli were clinically silent and the other 3 cases with back pain, diagnosis could not be made before FDG PET/CT because MRI was precluded.
3. There was a direct and significant impact on therapeutic care: antibiotic therapy was adapted and prolonged from 4 to 12 weeks in patients with spondylodiscitis.
4. A diagnosis of neoplasia was established in 3 patients, with a major impact on therapeutic care because these patients were asymptomatic.

In our cohort, we found that 29% of the 35 patients hospitalized for lead endocarditis had a septic embolism diagnosed by the FDG PET/CT scanning, including 20% with a diagnosis of spondylodiscitis. Interestingly, in 57% of spondylodiscitis diagnosis, there was no clinical suspicion before FDG PET/CT scanning. For the 43% remaining patients with

---

**TABLE 2** Baseline Characteristics of the 10 Lead Endocarditis Patients With Septic Emboli Identified by FDG-PET/CT Scanning

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Fever (°C)</th>
<th>CRP (mg/l)</th>
<th>Positive BC Pathogen</th>
<th>Positive TOE</th>
<th>Lead</th>
<th>Vegetation Size ≤ 10 mm</th>
<th>AB Before FDG PET/CT</th>
<th>Duration of AB Before FDG PET/CT*</th>
<th>FDG PET/CT Hotspots Septic Embolism</th>
<th>Lead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>8.5</td>
<td>Yes SE</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>4</td>
<td>Lungs</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>60.0</td>
<td>Yes St</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>Spondylodiscitis T2-L3</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>173.0</td>
<td>Yes EF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>40</td>
<td>Spondylodiscitis T2-L3 and L2-L3</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>339.0</td>
<td>Yes SA</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>60</td>
<td>Spondylodiscitis T7</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>193.0</td>
<td>Yes OS</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>Spondylodiscitis C5-C7, T4-T5, and T6-T7</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>181.3</td>
<td>Yes SE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>30</td>
<td>Spondylodiscitis L2-L3</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>100.4</td>
<td>Yes SA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>33</td>
<td>Spondylodiscitis L4-L5 and psoas abscess</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>109.1</td>
<td>Yes OS</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>14</td>
<td>Proximal extremity of the aortobifemoral prosthesis</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>117.0</td>
<td>No SA</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>Spondylodiscitis C5-C6</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>155.0</td>
<td>Yes SE</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>30</td>
<td>Lungs</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Duration of AB before FDG PET/CT is expressed in days.

**TABLE 3** Comparison Between the Septic and Nonseptic Emboli Groups

<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>70 ± 15</th>
<th>74 ± 18</th>
<th>0.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1 (10)</td>
<td>3 (12)</td>
<td>1.00</td>
</tr>
<tr>
<td>Fever</td>
<td>8 (80)</td>
<td>13 (52)</td>
<td>0.25</td>
</tr>
<tr>
<td>C-reactive protein levels, mg/l</td>
<td>144 ± 90</td>
<td>67 ± 61</td>
<td>0.011</td>
</tr>
<tr>
<td>Positive BC</td>
<td>10 (100)</td>
<td>17 (68)</td>
<td>0.07</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3/10 (30)</td>
<td>1/17 (6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>3/10 (30)</td>
<td>8/17 (47)</td>
<td>0.69</td>
</tr>
<tr>
<td>Positive TOE findings</td>
<td>7 (70)</td>
<td>16 (64)</td>
<td>1.0</td>
</tr>
<tr>
<td>Presence of vegetation</td>
<td>7 (70)</td>
<td>14 (56)</td>
<td>0.70</td>
</tr>
<tr>
<td>Vegetation size ≥ 10 mm</td>
<td>2 (20)</td>
<td>6 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>AB before FDG PET/CT</td>
<td>9 (90)</td>
<td>18 (72)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Values are mean ± SD or n (%). Means and proportions comparisons used nonparametric tests such as Mann-Whitney U test or Fisher exact test, respectively. Quartiles (Q1, Q2 and Q3) are given for C-reactive protein. Abbreviations as in Tables 1 and 2.
spondylodiscitis presenting with dorsal pain before FDG PET/CT scanning, the diagnosis could not be confirmed by alternative imaging modalities. Indeed, MRI is considered as the reference diagnostic tool when the suspicion remains after negative x-rays and CT scanning and cannot be performed in the vast majority of patients with implantation of pacing leads. However, the positive predictive value of FDG PET/CT in patients with suspected infectious spondylodiscitis is known to be very high (23). Identification and confirmation of spondylodiscitis with FDG PET/CT scanning had an important impact on the therapeutic pathway because antimicrobial therapy was prolonged from 4 to 12 weeks with special attention paid to neurologic clinical examination. In the published data, the incidence of spondylodiscitis is lower (5% to 11% in patients with lead endocarditis). However, this diagnosis has not been systematically searched for in patients without clinical vertebral signs.

Surprisingly, a diagnosis of neoplasia was suspected in approximately 10% of patients after FDG PET/CT scanning (24). It had also a major impact in the therapeutic pathway for these polypathologic patients. This surprising high incidence might be incidental but may also be explained by the age of our cohort (73 ± 13 years). Moreover, the presence of neoplasia is a recognized risk factor for relative immunodeficiency and might have contributed to the infective risk in the patients studied (25).

A non-negligible percentage of patients with infectious endocarditis may experience a recurring episode (17). Thus, identifying and treating the portal of entry is important. We did not establish a direct link between the gastrointestinal tract lesions identified on FDG-PET and the endocarditis. Nevertheless, colonic lesions (polyps, diverticulosis, adenocarcinoma) are among potential portals of entry (26).

Findings from the present prospective study in patients with pacing lead endocarditis confirm the importance of FDG PET/CT staging in patients with suspected infective endocarditis (27,28). In this study, the observed high rate of additional diagnosis and the associated clinical implications may suggest systematic integration of FDG PET/CT scanning in the
diagnostic algorithm of patients with lead endocarditis. The potential disadvantages of this diagnostic tool are its relatively high cost and its limited availability. However, FDG PET/CT scanning may prove to be cost effective because it dramatically changes the therapeutic care pathway in some patients. In addition, scintigraphy with labeled white blood cells has advantages in some situations of suspected infection offering high specificity (29). However, in spondylodiscitis, it lacks sensitivity. This is a major advantage for FDG PET/CT in this setting.

STUDY LIMITATIONS. This is a pilot study with a limited number of lead endocarditis patients, which does not allow the formulation of definitive conclusions concerning the role of the FDG PET/CT scanning for the diagnosis of septic embolism. Our results must be confirmed in a larger study.

FDG PET/CT scanning has been advocated as a promising tool for the diagnosis of lead endocarditis. Assessment of the sensitivity, specificity, and prognostic values were not the aim of the present study and only patients with device infection and referred for extraction were included. Also, because the main purpose was searching for septic emboli, no specific low-carbohydrate regimen was used to drastically reduce myocardial uptake. Although 77% of patients were being treated with antibiotics at the time of their FDG PET/CT studies, FDG uptake along the lead was found in 54% (19 of 35) which is in line with findings from others (30,31).

We performed PET/CT 1 h after FDG administration in agreement with The European Association of Nuclear Medicine/The Society of Nuclear Medicine and Molecular Imaging Guidelines for FDG PET in inflammation or infection (32). However, the optimal imaging time in the setting of infective endocarditis is not yet clear. Some studies in the setting of infection have found dual-time-point imaging useful (33,34). Leccisotti et al. (33) assessed the diagnostic

Transaxial CT views (A, B, and C), FDG PET views (D, E, and F), and fused PET/CT views (G, H, and I) at the level of the pacing lead, the superior mediastinum, and the aortobifemoral vascular prosthesis. There is an increased FDG uptake in the intracardiac portion of the right ventricular lead (arrows in D and G) corresponding to lead endocarditis. An important hotspot was also identified in the superior mediastinum (arrows in E and H), corresponding to a large esophageal neoplasm with important extension. A septic embolism was seen in the proximal part of the aortobifemoral prosthesis (arrows in F and I). Abbreviations as in Figure 1.
accuracy of delayed (3 h) compared to standard (1 h) FDG PET/CT imaging in cardiac implantable electronic device infection. The diagnostic accuracy of delayed imaging was significantly higher than 1-h scan for lead infection (70% vs. 51%, p = 0.024). No significant difference was found regarding pocket or device infection. They concluded that delayed FDG PET/CT imaging would be helpful, at least in patients with a negative 1-h scan. The value of delayed imaging and retention index deserves to be assessed in a large prospective series of infective endocarditis.

FDG PET/CT has proven its clinical value and cost-effectiveness in diagnosing metastatic infections in patients with gram-positive bacteremia. In the study by Vos et al. (35), the incidence of metastatic infection uncovered with FDG PET/CT was similar in patients with Streptococcus species and patients with S. aureus bacteremia. Sensitivity might be lower for intracellular bacteria, Coxiella burnetii (Q fever), HACEK group organisms, and pathogens that escape the immune system. Large series are needed in the setting of patients with pacemaker lead endocarditis to examine the sensitivity of FDG PET/CT according to the type of causative pathogen.

Spondylodiscitis patients were treated with antibiotics for a 12-week duration, in accordance with the guidelines at the time of the study. Recently, 6 weeks of antibiotics have been advocated (36) in localized and noncomplicated spondylodiscitis with favorable prognostic factors. This is still a longer duration compared to the 4 weeks duration in patients with lead endocarditis (and without septic emboli).

Although we considered infection in the vascular aortobifemoral prosthesis in 1 patient as septic embolus, it might be that the prosthesis was the portal of entry for endocarditis. Whatever the exact sequence, detection of the occult vascular prosthesis infection with FDG was of importance.

CONCLUSIONS

This study shows the potential value of FDG PET/CT scanning in the diagnosis of septic emboli in patients with pacing lead endocarditis. This promising diagnostic tool may be integrated in the diagnostic algorithm of patients with lead endocarditis because diagnosis of septic embolisms has a direct and significant impact on the therapeutic care pathway.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Lead endocarditis is associated with important morbidity due to septic emboli. However, the diagnosis may be difficult because MRI cannot be performed in most cases. FDG PET/CT scanning may have a critical role in identifying septic emboli in patients with lead endocarditis.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Spondylodiscitis was identified in 20% of patients with lead endocarditis, including 57% clinically silent, with a direct and significant impact on therapeutic care (prolonged antibiotics with bone penetration). In addition, a tumor diagnosis was suspected in 14% with a major impact as these patients were asymptomatic.

TRANSLATIONAL OUTLOOK: Given the observed high rate of additional diagnosis and the associated clinical implications, systematic integration of FDG PET/CT scanning in the diagnostic algorithm of patients with lead endocarditis may be warranted.

REFERENCES

FDG PET/CT Imaging, Septic Emboli, and Lead Endocarditis


KEY WORDS FDG PET/CT scanning, lead endocarditis, pacemaker infection, septic emboli, spondylodiscitis