Accuracy of ^{18}F-FDG PET/CT in patients with the suspicion of cardiac implantable electronic device infections

Adrián Jerónimo, MD,[a] Carmen Olmos, MD, PhD,[a] Isidre Vilacosta, MD, PhD,[a] Aida Ortega-Candil, MD, PhD,[b] Cristina Rodríguez-Rey, MD, PhD,[b] María Jesús Pérez-Castejón, MD, PhD,[b] Cristina Fernández-Pérez, MD, PhD,[c] Carlos Nicolás Pérez-García, MD,[a] Daniel García-Arribas, MD,[a] Carlos Ferrera, MD, PhD,[a] and José Luis Carreras, MD, PhD[b]

[a] Instituto Cardiovascular, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdSSC), Madrid, Spain

[b] Servicio de Medicina Nuclear, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdSSC), Madrid, Spain

[c] Servicio de Medicina Preventiva, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdSSC), Universidad Complutense de Madrid, Madrid, Spain

Received Apr 25, 2020; accepted Jun 28, 2020
doi:10.1007/s12350-020-02285-z

Background. **Utility of ^{18}F-FDG PET/CT in diagnosing infective endocarditis (IE) associated with cardiac implantable electronic devices (CIEDs) is not well established. Current ESC guidelines recommend the use of FDG-PET imaging in patients with CIEDs and positive blood cultures, but the number of studies evaluating the diagnostic performance of FDG-PET imaging in these patients remain limited. Our objective was to assess the diagnostic yield of ^{18}F-FDG PET/CT in patients with suspected CIED infections, differentiating between pocket infection (PI) and lead infection (CIED-IE).**

Methods and Results. **From 2013 to 2018, all patients (n = 63) admitted to a hospital with suspected CIED infection were prospectively recruited, undergoing a diagnostic work-up including a PET/CT. Explanted devices and material from the pocket were cultured. 14 cases corresponded to isolated PI and 13 were categorized as CIED-IE. Considering radionuclide uptake in the intracardiac portion of the lead, sensitivity and specificity of PET/CT for CIED-IE were 38.5% and 98.0%, respectively. Positive (19.2) and negative (0.6) likelihood ratio values, suggest that a positive PET/CT is much more probable to correspond to a patient with CIED-IE, whereas it is not possible to exclude this diagnosis when negative. For PI, sensitivity and specificity were 72.2% and 95.6%, respectively.**

Conclusions. **The yield of ^{18}F-FDG PET/CT for suspected CIED infections differs depending on the site of infection. Due to very high specificity but poor sensitivity, negative studies must be interpreted with caution if the suspicion of CIED-IE is high. (J Nucl Cardiol 2022;29:594–608.)**

Key Words: Infection • PET • diagnostic and prognostic application

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12350-020-02285-z) contains supplementary material, which is available to authorized users.

The authors of this article have provided a PowerPoint file, available for download at SpringerLink, which summarizes the contents of the paper and is free for re-use at meetings and presentations. Search for the article DOI on SpringerLink.com.

The authors have also provided an audio summary of the article, which is available to download as ESM, or to listen to via the JNC/ASNC Podcast.

Funding There was no specific funding for this manuscript.

Reprint requests: Carmen Olmos, MD, PhD, Instituto Cardiovascular, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdSSC), Madrid, Spain; *carmen.olmosblanco@gmail.com*

1071-3581/$34.00

Abbreviations	
CIED	Cardiac implantable electronic devices
^{18}F-FDG	Fluor-18-fluorodeoxyglucose
IE	Infective endocarditis
PET/CT	Positron emission tomography/computed tomography
PI	Pocket infection
TTE	Transthoracic echocardiography
TEE	Transesophageal echocardiography

See related editorial, pp. 609–611

INTRODUCTION

Fluor-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has lately emerged as a new technique to diagnose prosthetic valve infective endocarditis, IE.[1–3] Different studies have evaluated the role of this tool in patients with cardiac implantable electronic device (CIED) infections, especially in pocket infections, PI.[4–7] However, the usefulness of this imaging technique in CIED-IE is not well established.[6,7]

A prospective cohort study was performed to assess the diagnostic yield of ^{18}F-FDG PET/CT in patients with suspected CIED infections. Special emphasis was placed on differentiating between pocket and lead infection.

METHODS

Patient Population

From January 2013 to December 2018, all patients admitted to our tertiary care hospital with suspected CIED infection were prospectively recruited on a multipurpose database. The protocol was approved by the Local Ethical Committee and patients' informed consent was obtained.

All patients were evaluated by the Endocarditis Team and underwent a thorough diagnostic work-up that included a detailed clinical history and physical examination, electrocardiography, blood analysis, blood cultures at admission and 48-72 hours later, transthoracic (TTE) and transesophageal echocardiography (TEE), and a PET/CT. An initial classification of episodes according to modified Duke Criteria as *rejected*, *possible*, and *definite* CIED-IE was established. In those patients in whom devices required explantation, endovascular lead extraction was the approach of choice. Material from the device pocket, generator and leads were systematically cultured.

^{18}F-FDG PET/CT: Study Protocol and Image Analysis

^{18}F-FDG PET/CT studies were preferably carried out in the first 72 hours after the diagnostic suspicion was established, but delay was not an exclusion criterion. The studies were performed according to the EANM guidelines,[8] as has been previously described in detail elsewhere.[9,10] ^{18}F-FDG was administered at a dose of 5 MBq·kg^{-1} body weight using an automatic injector, and patients rested in a quiet room for 50-60 minutes before images acquisition.

To reduce physiological myocardial uptake of ^{18}F-FDG, all patients consumed a low-carbohydrate high-fat diet during 48 hours before the procedure and fasted for 12 hours.

Attenuation-corrected (AC) and non-attenuation-corrected (NAC) images were examined by two nuclear physicians blinded to the clinical and microbiological information, and the analysis of the images was made based on visual interpretation and semi-quantitative evaluation.[9]

Visual analysis considered abnormal (positive) the presence of ^{18}F-FDG uptake in AC images that persisted in NAC images. Semi-quantitative evaluation measured the maximum standardized uptake value (SUV_{max}) in the abnormal area, and the target-to-background standardized uptake value ratio (SUV_{ratio}). Extracardiac ^{18}F-FDG uptakes indicating embolic events (especially in the lungs), alternative diagnoses and incidental lesions were carefully searched.

Gold Standard for Diagnosis of CIED-IE

(1) The gold standard for CIED-IE was a positive lead culture in the absence of PI when percutaneous extraction was performed or a positive culture from a surgically removed lead.
(2) In spite of negative lead cultures, the presence of typical TEE images of vegetations in a clinical context of positive blood cultures was also considered a major criterion for CIED-IE.[11]
(3) Pulmonary embolisms detected by PET/CT in the context of fever without a clear focus of infection and the presence of vegetations on TEE images or positive blood cultures.

Gold Standard for Diagnosis of PI

(1) Positive generator culture with or without the presence of wound inflammation with cellulitis, swelling, or purulent exudate affecting the generator site and
(2) Absence of lead involvement (lead vegetations or positive lead cultures).

A minimum of 6-month follow-up was performed in patients in whom infection was rejected.

Statistical Analysis

Quantitative variables were expressed as median and interquartile range (IQR) or mean and standard deviation (SD). Assessment of normality and equality of variances for continuous data was performed using the Shapiro–Wilk test and the Levene test, respectively. Continuous variables were compared with a Student's t test, Fisher-Pittman permutation test or median test when appropriate. Categorical variables are expressed as frequencies and percentages.

The results of ^{18}F-FDG PET/CT were compared with the gold standard diagnosis of each episode. Subsequently, sensitivity, specificity, positive and negative likelihood ratios and predictive values with their 95% confidence intervals were calculated using the final diagnosis of *confirmed* or *rejected* CIED-IE and PI.

Receiver-operating characteristic (ROC) curves were used to determine the cut-off values of PET/CT semi-quantitative analysis with the best sensitivity-specificity combination to detect infection (definite vs non-definite).

All tests were two-sided and differences were considered statistically significant at P-values $< .05$. Statistical analyses were performed with Stata/IC12.1 (StataCorp, College Station, Texas, USA).

RESULTS

Study Population

63 Patients with suspicion of CIED infection were prospectively included in the study. Median age was 77.5 (70.4-83.3) years old and 43 (68.3%) of them were male. 48 (76.2%) Patients carried a pacemaker; 6 (9.5%) patients had an implantable cardioverter defibrillator (ICD); 1 (1.6%) patient had a cardiac resynchronization therapy (CRT) device, and 8 (12.7%) patients had an ICD/CRT. Median time between device implantation and PET-CT study was 2.3 (0.6-6.4) years.

Most patients presented with persistent fever (n = 42, 67.7%), 12 (19%) had local signs of infection, and 4 (6.3%) had skin erosion without concomitant signs of inflammation.

All patients underwent at least one TTE and one TEE, as well as blood cultures. 30 patients (57.1%) had positive blood cultures fulfilling a major Duke criterion. Coagulase-negative staphylococci were the most frequent isolated microorganisms (n = 14; 35.0%), followed by *Enterococcus faecalis* (n = 8; 20.0%) and *Staphylococcus aureus* (n = 7; 17.5%) (Table 1).

TEE documented typical lead vegetations in 12 (19.0%) patients. Thus, Duke criteria initially classified 24 patients as *rejected CIED-IE*, 23 as *possible CIED-IE*, and 16 as *definite CIED-IE*.

26 (41.3%) patients underwent device extraction together with cultures of the explanted materials, which resulted positive in 18 (69.2%) of them. In 4 cases microorganisms were exclusively isolated in the device generator, whereas in 3 patients only the leads resulted positive. Both components of the device, leads and generator, were concomitantly positive in 11 patients. In one of these 11 patients, the isolated microorganisms differed between generator and lead cultures.

After finishing the diagnostic work-up, including PET/CT, 14 patients were finally diagnosed with isolated PI, and 13 patients were categorized as CIED-IE.

Table 1. Microorganisms isolated in blood cultures

	n = 42
Coagulase-negative staphylococci	14 (35%)
Enterococcus faecalis	8 (20%)
Staphylococcus aureus	7 (17.5%)
Streptococcus gallolyticus	3 (7.5%)
Gram-negative bacilli	3 (7.5%)
Enterococcus faecium	2 (5.0%)
Viridans group streptococci	2 (5.0%)
Streptococcus agalactiae	1 (2.5%)
Coxiella burnetii	1 (2.5%)
Candida parapsilosis	1 (2.5%)

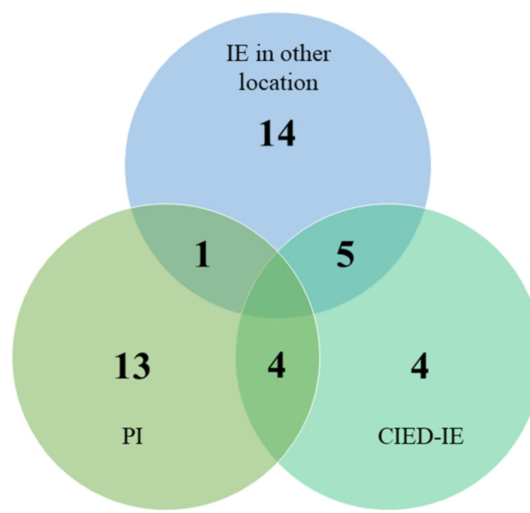

Figure 1. Distribution of patients diagnosed with CIED-IE, PI or left-sided IE. *CIED*, cardiac implantable electronic device; *IE*, infective endocarditis; *PI*, pocket infection.

Four of these 13 patients had both PI and CIED-IE. In addition, concomitant left-sided IE was diagnosed in 1 case of PI and in 5 cases of CIED-IE (Figure 1). The final diagnosis in those patients in whom both PI and CIED-IE were ruled out is summarized in Table 2. Importantly, 31.7% of our cohort had IE in other locations (Table 2, Online Resource 1).

Diagnostic criteria fulfilled by those 13 patients with CIED-IE are shown in Table 3. Two patients had positive lead cultures in the absence of positive generator cultures, 7 patients had lead vegetations documented on TEE in the context of positive blood cultures (1 of these patients also had pulmonary embolisms on PET/CT), and 2 patients had both positive

Table 2. Final diagnosis in patients in whom PI and CIED-IE were ruled out

	n = 36
IE in other location	14 (38.9%)
Bacteremia without an evident focus	6 (16.7%)
Urinary tract infection	5 (13.9%)
Phlebitis	2 (5.6%)
Skin erosion without infection	2 (5.6%)
Pacemaker scar inflammation without infection	2 (5.6%)
Still's disease	1 (2.8%)
Upper respiratory tract infection	1 (2.8%)
Fever of unknown origin	2 (5.6%)
Other*	1 (2.8%)

CIED, cardiac implantable electronic device; *IE*, infective endocarditis; *PI*, pocket infection
*PET/CT was performed to rule out endocarditis in a case with new-onset periprosthetic aortic regurgitation

Table 3. Diagnostic findings used as gold standard of CIED-IE

	n = 13
Positive lead cultures without PI	4 (30.8%)
Lead vegetations on TEE and positive blood cultures	9 (69.2%)
Pulmonary embolisms and positive blood cultures or lead vegetations	2 (15.4%)

CIED, cardiac implantable electronic device; *IE*, infective endocarditis; *PI*, pocket infection; *TEE*, transesophageal echocardiography

lead cultures and TEE images of lead vegetations. In one of them, pulmonary embolisms were also identified by PET/CT (Figure 2).

The initial patients' classification according to modified Duke criteria and the final consensus diagnosis for CIED-IE are presented in Figure 4. The distribution of patients among definite, possible or rejected IE depending on PET/CT results as an additional major criterion, in comparison with the final diagnostic consensus after follow-up, is shown in Table 4. Additional information about main clinical features and diagnostic tests of all patients is summarized in Online Resource 2, attached as Supplementary Materials.

PET/CT Performance

53 (85.5%) patients were receiving antibiotic therapy when PET/CT was performed. Median time of antibiotic treatment before performing the PET/CT study was 7 (2-15) days.

PET/CT detected an abnormal ^{18}F-FDG uptake in the pocket region of the electronic device in 16 (25.4%) patients. 21 (33.3%) patients had an abnormal uptake in the extracardiac portion of the lead, close to the generator pocket, and 6 (9.5%) of them simultaneously showed an abnormal radionuclide uptake in the intracardiac segment of the lead.

Measures to reduce physiological radionuclide uptake by the myocardium were successful in 58 (92.0%) patients. However, all 5 patients in whom low-carbohydrate high-fat diet and prolonged fasting resulted ineffective, had a true negative PET/CT study.

For the purpose of analyzing the predictive performance of ^{18}F-FDG uptake in the different segments of the lead (intracardiac portion vs any portion of the lead) for the diagnosis of CIED-IE, sensitivity and specificity for each type of uptake was evaluated.

^{18}F-FDG uptake in the intracardiac portion of the lead for the diagnosis of CIED-IE Only 5 out of 13 patients with definite CIED-IE had abnormal ^{18}F-FDG uptake in the intracardiac portion of the lead. The remaining 8 cases of CIED-IE had false negative PET/CT studies.

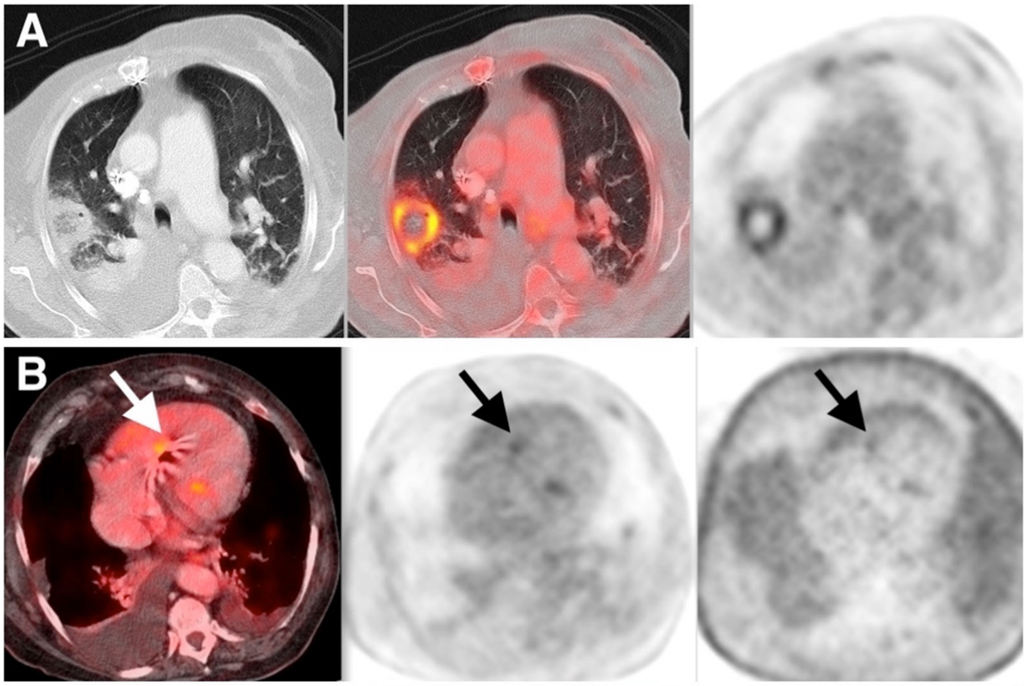

Figure 2. Pulmonary embolism documented by PET/CT in a patient with CIED-IE. (**A**) ^{18}F-FDG PET/CT axial views of a patient with pacemaker IE due to *S. aureus* showing a subpleural nodular lung opacity in the right upper lobe with central low attenuation region and intense FDG uptake in its periphery suggestive of pulmonary embolism. Transesophageal echocardiography showed a 1 cm vegetation attached to the lead. (**B**) Axial PET/CT view showing fusion (left), PET attenuation correction (middle) and PET non attenuation correction images (right) showing focal FDG intracardiac pacemaker lead uptake (arrows). *CIED*, cardiac implantable electronic device; *IE*, infective endocarditis.

Potential sources of false negatives were carefully analyzed. However, we did not find any significant differences between false negatives and true positive cases in vegetation size, antibiotic treatment duration prior to PET/CT, antibiotic treatment duration prior to device removal, time elapsed between PET/CT and device extraction, or systemic inflammatory activity (Table 5).

On the other hand, there was only one patient showing abnormal ^{18}F-FDG uptake at the intracardiac portion of the lead in the absence of CIED-IE (false positive). This patient had undergone surgical aortic valve replacement together with a pacemaker implantation less than a month before PET/CT was performed. Even though he presented with fever and doubtful images on TEE, blood cultures resulted negative and the final diagnosis was an upper respiratory tract infection.

^{18}F-FDG uptake in the extracardiac portion of the lead for the diagnosis of CIED-IE Considering ^{18}F-FDG uptake in the extracardiac portion of the lead for the diagnosis of CIED-IE, only 2 out of 15 patients with radionuclide uptake only in the extracardiac segment of the lead (without any significant uptake in the intracardiac portion) had a final diagnosis of CIED-IE. In both cases, CIED-IE diagnosis was established by echocardiographic criteria and they had a concomitant PI.

Diagnostic accuracy of PET/CT for CIED infection Sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values and global diagnostic accuracy of PET/CT for lead infection (considering any lead uptake or only intracardiac uptake), as well as for PI (considering pocket uptake or extracardiac lead uptake) are shown in Table 6.

When only the intracardiac portion of the lead is taken into account, the sensitivity of PET/CT is low (38.5%). The presence of ^{18}F-FDG uptake at any segment of the lead increased sensitivity by 15%, but at the expenses of a notorious increase of PET/CT false positives with the consequent decrease of specificity, positive predictive value and global accuracy. The explanation to this fact rests on 13 out of 15 cases with a positive PET/CT at any portion of the lead having a PI

Table 4. Comparison of Duke criteria at admission, ^{18}F FDG PET/CT, and modified Duke criteria including results of PET/CT, and final diagnostic consensus after follow-up for CIED-IE

		Final diagnosis after follow-up (IE team consensus) for lead infection (CIED-IE)	
		Definite 13	**Rejected 50**
Modified Duke criteria at admission			
Definite IE	16	10 (62.5%)	6 (37.5%)
Possible IE	23	3 (13.0%)	20 (87.0%)
Rejected IE	24	0 (0%)	24 (100%)
^{18}F FDG PET/CT			
Positive	6	5 (83.3%)	1 (16.7%)
Negative	57	8 (14.0%)	49 (86.0%)
Modified Duke criteria + ^{18}F FDG PET/CT			
Definite IE	16	10 (62.5%)	6 (37.5%)
Possible IE	24	3 (12.5%)	21 (87.5%)
Rejected IE	23	0 (0%)	23 (100%)

For the purpose of this analysis, only FDG in the intracardiac portion of the lead has been considered
CIED, cardiac implantable electronic device; *^{18}F-FDG*, fluor-18-fluorodeoxyglucose; *IE*, infective endocarditis; *PET/CT*, positron emission tomography/computed tomography

Table 5. Analysis of potential factors influencing PET/CT diagnostic yield

	False negatives*	True positives*	*P*
Vegetation mean size (mm)	20 (11-30)	13 (11-15)	.295
Antibiotic treatment duration prior to PET/CT (days)	15 (11-44)	11 (1-11)	.242
Antibiotic treatment duration prior to device extraction (days)	17 (14-18)	14 (7-15)	.853
Time between PET/CT and device extraction (days)	3.5 (1-4)	4 (4-6)	.999
C-reactive protein levels (mg·L^{-1})	2.8 [1.0]	5.2 [2.6]	.355
C-reactive protein levels > 40 mg·L^{-1}	60%	40%	.679
Leukocyte count (mm^3)	27,338 [899]	7,760 [3,109]	.876

PET/CT, positron emission tomography/computed tomography
*Values are median (interquartile range) or mean (standard deviation)

with local extension of radionuclide uptake to the most proximal part of the lead (PET/CT false positives). The other 2 PET/CT positive patients had pocket and lead infection simultaneously (PET/CT true positives).

Thus, according to the positive likelihood ratio, a positive result of PET/CT is 19.2 times more probable to correspond to a patient with CIED-IE than to a patient without CIED-IE. On the other hand, the negative likelihood ratio (0.6) suggests that it is not possible to exclude the diagnosis of CIED-IE when PET/CT is negative (Figure 3).

A positive PET/CT result did not modify the final diagnosis of IE in any case (Figure 4).

The case of PI is different. Both pocket and extracardiac portion of the lead ^{18}F-FDG uptake had fair sensitivity and good specificity, although the latter obtained higher values in both parameters, and better global diagnostic accuracy (Table 6; Figure 5).

Semi-quantitative analysis Median pocket and lead SUV_{max} and SUV_{ratio} values according to patients' final classification (absence of infection, PI, and lead infection) are shown in Table 7. Significant

Table 6. Diagnostic yield of PET/CT for the diagnosis of pocket and lead cardiac implantable electronic device infection

	PI (n = 18*)		Lead infection (n = 13*)	
	Pocket ^{18}F-FDG uptake	**Extracardiac portion of the lead ^{18}F-FDG uptake**	**Intracardiac portion of the lead ^{18}F-FDG uptake**	**Any portion of the lead ^{18}F-FDG uptake**
True positives	11	13	5	7
False positives	5	2	1	14
True negatives	40	43	49	36
False negatives	7	5	8	6
Sensitivity	61.1% (38.6%-79.7%)	72.2% (49.1%-87.5%)	38.5% (17.7%-64.5%)	53.8% (29.1%-76.8%)
Specificity	88.9% (76.5%-95.2%)	95.6% (85.2%-98.8%)	98.0% (89.5%-99.6%)	72.0% (58.3%-82.5%)
Positive likelihood ratio	5.5 (2.2-13.6)	16.3 (4.1-64.9)	19.2 (2.5-150.7)	1.9 (1.0-3.8)
Negative likelihood ratio	0.4 (0.2-0.8)	0.3 (0.1-0.6)	0.6 (0.4-1.0)	0.6 (0.3-1.2)
Positive predictive value	68.8% (44.4%-85.8%)	86.7% (62.1%-96.3%)	83.3% (43.6%-97.0%)	33.3% (17.2%-54.6%)
Negative predictive value	85.1% (72.3%-92.6%)	89.6% (77.8%-95.5%)	86.0% (74.7%-92.7%),	85.7% (72.2%-93.3%)
Global diagnostic accuracy	81.0% (69.6%-88.8%)	88.9% (78.8%-94.5%)	85.7% (75.0%-92.3%)	68.3% (56.0%-78.4%)
AUC	0.750 (0.621-0.847)	0.839 (0.727-0.921)	0.682 (0.553-0.794)	0.629 (0.504-0.753)

PI, pocket infection
*Patients with both PI and lead infection were accounted independently in each scenario

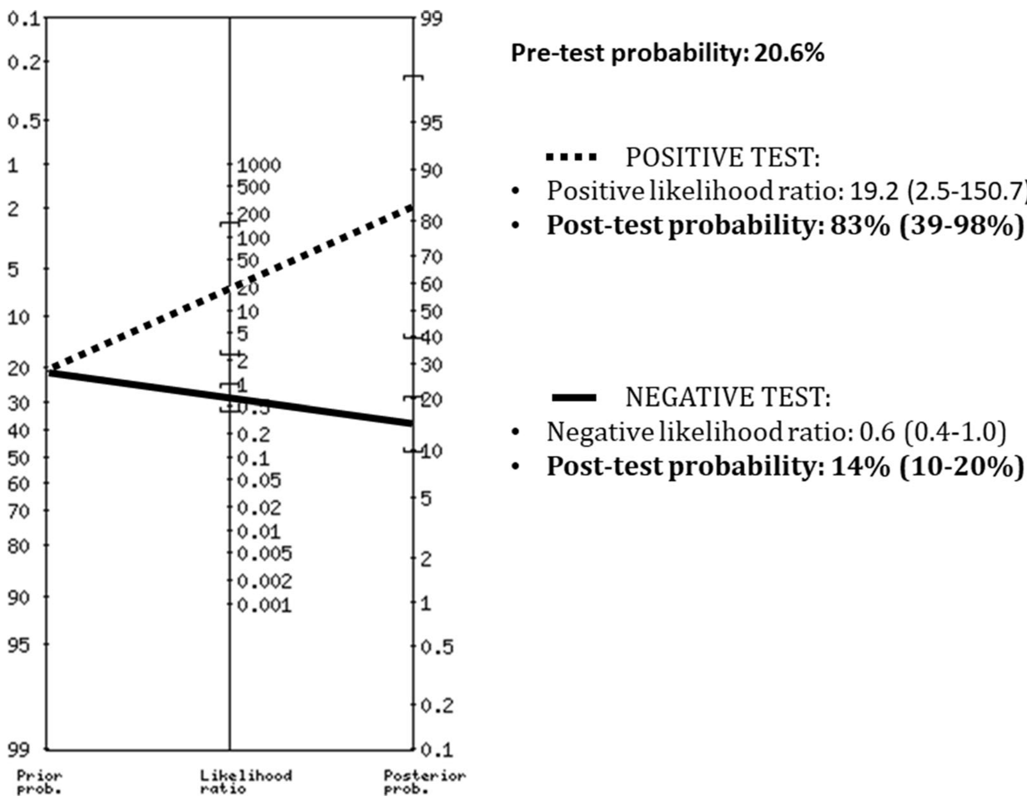

Figure 3. Post-test probabilities for diagnosis of CIED-IE applying positive and negative likelihood ratios (Fagan nomogram). *CIED*, cardiac implantable electronic device; *IE*, infective endocarditis.

differences were found in extracardiac lead SUV_{max} and SUV_{ratio} when comparing patients without CIED infection and those with PI and CIED-IE.

The predictive performance of both extracardiac lead SUV_{max} and SUV_{ratio} in PI were good, with an area under the ROC curve (AUC) of 0.870 (0.726-0.957), and 0.879 (0.733-0.968), respectively. Cut-off points with the best sensitivity-specificity relationship, as well as with 100% specificity to confirm PI are represented in Figure 6. On the contrary, the predictive performance of semi-quantitative analysis for the diagnosis of CIED-IE was poor (AUC < 0.65) and, due to the low sensitivity of PET/CT, cut-off values were not useful in this setting.

DISCUSSION

Over the last 10 years, along with progressive aging of the population, the number of CIED implantations has increased, and so have their complication rates. According to the literature, the incidence rate of CIED-IE is 1.1 per 1,000 device-years,[12] and it is associated with a significant risk of death and considerable comorbidity.[4]

TEE plays an essential role in the diagnosis of patients with CIED-IE, not only for the detection of vegetations, but also for the assessment of tricuspid valve involvement and function. However, vegetations cannot always be differentiated from lead strands or thrombi; and frequently, patients with transvenous electrode leads have lead-associated masses without proven infection.[13] In addition, a normal TEE study does not rule out CIED-IE,[11] and it is well known that Duke criteria have lower sensitivity in CIED-IE than in other clinical scenarios.[3,11] For all these reasons, other diagnostic techniques, such as PET/CT, might have a complementary role in the diagnosis of CIED-IE. The usefulness of this imaging technique in patients with CIED infections has been evaluated in several studies,[2,4–7,14–17] with good results, but most series included predominantly or even exclusively local PI.

Diagnostic Accuracy of PET/CT

The present study comprises the largest prospective cohort of patients with suspected CIED infections to date in which the diagnostic accuracy of PET/CT has

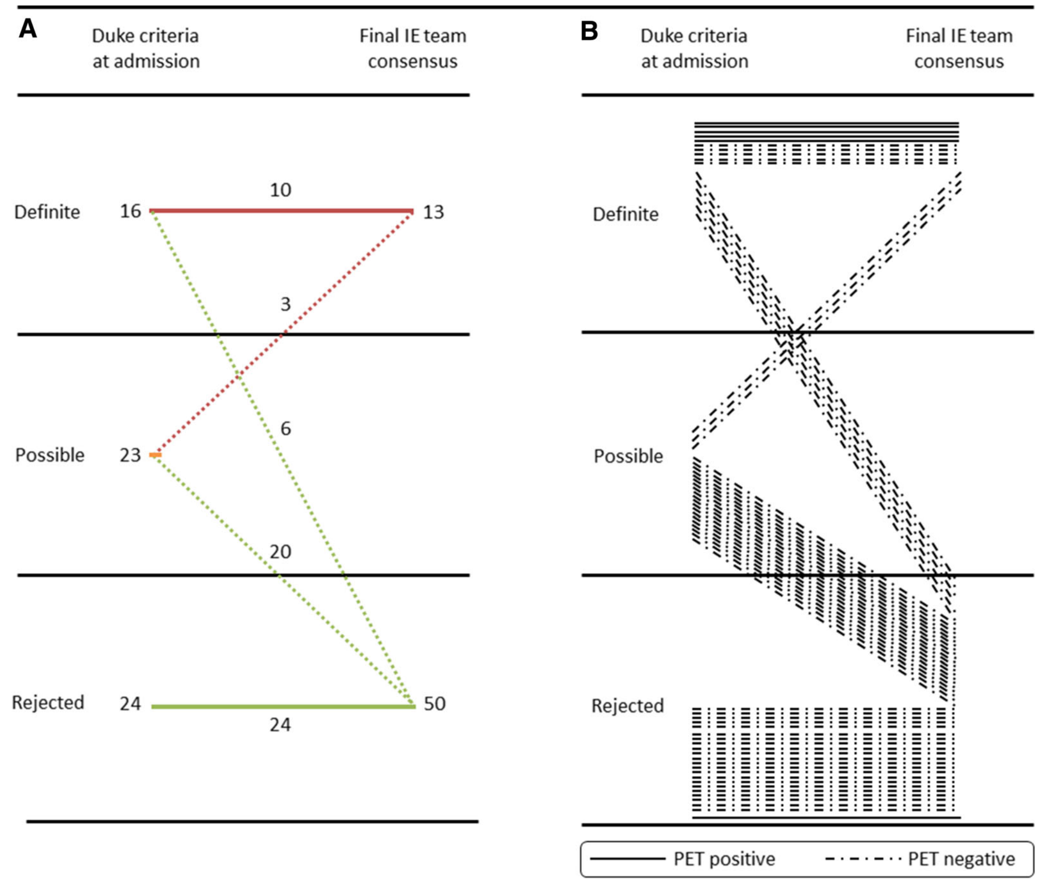

Figure 4. Comparison of Duke criteria at admission and final diagnostic consensus after follow-up, and PET/CT results. (**A**) Classification of CIED-IE episodes at admission and after follow-up. (**B**) Individual PET/CT results in relation to initial Duke criteria and final diagnostic consensus. Each patient is represented by a single line. *CIED*, cardiac implantable electronic device; *IE*, infective endocarditis.

been analyzed. Our study is unique for several reasons: (1) all patients were prospectively collected and evaluated by the Endocarditis Team; (2) at least one TEE was performed in all cases; (3) the prevalence of IE in our cohort was very high, as 38.9% of patients had a final diagnosis of valvular IE, and the proportion of patients with a final diagnosis of CIED-IE was higher (20.6%) than that described in previous studies; (4) the sensitivity and specificity of ^{18}F-FDG uptake in both the pocket and the leads (intra and extracardiac), have been assessed; and (5) a very precise definition of CIED-IE and generator infection and their reference gold standards have been applied.

The first universally agreed definitions for the diagnosis of CIED infections have recently been established.[18] So far, The British Society for Antimicrobial Chemotherapy guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection distinguished between uncomplicated generator pocket wound inflammation, uncomplicated and complicated generator PI, and isolated CIED lead infection (with and without evidence of generator PI).[19] On the other hand, the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of IE differentiated between local device infection and CIED-IE, in which the infection has extended to the electrode leads, valve leaflets or endocardial surface.[3]

In our study, the latter definition has been applied, due to its greater simplicity and practical implications. ESC guidelines remark that the distinction between the two entities is not always easy, as intraoperative contamination of the leads in patients with PI may occur during system extraction. For this reason, the gold standard applied in our cohort for the diagnosis of CIED-IE was the isolation of microorganisms in the intracardiac portion of the leads in the absence of positive pocket cultures or when the lead was surgically removed. In cases with negative lead cultures, or when

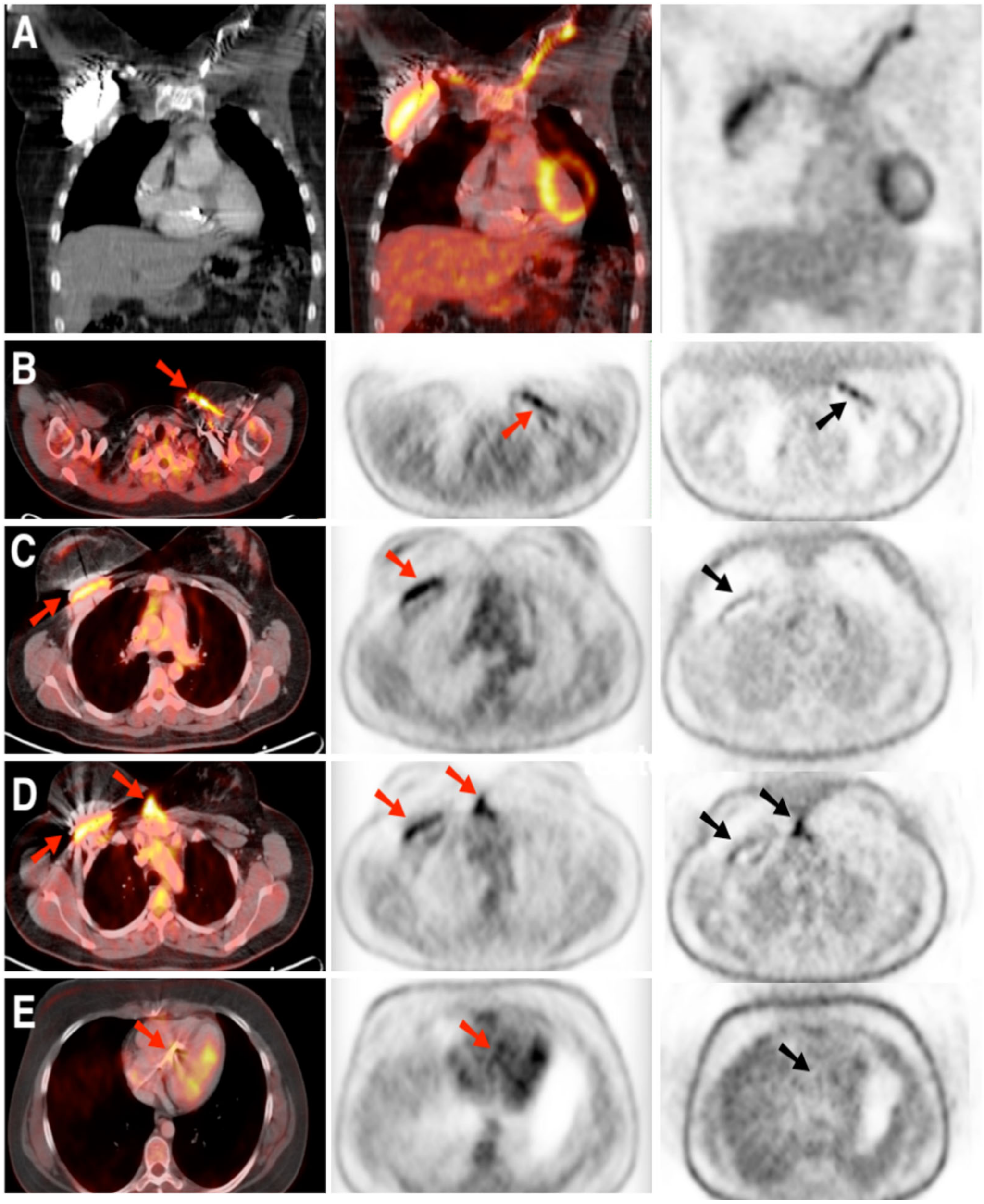

Figure 5. PI documented by PET/CT. (**A**) Coronal CT (left), PET/CT (center) and PET (right) images displaying a positive study for PI. (**B**) Axial PET/CT image (left), attenuated-corrected (AC) PET image (center) and non-attenuated-corrected (NAC) PET image (right) showing intense ^{18}F-FDG uptake along the subcutaneous pathway of the electrode (red and black arrows, respectively) and in the generator pocket (images **C** and **D**). Persistent radionuclide uptake in NAC images suggests an active inflammatory/infectious process, ruling out overcorrection artifacts. (**E**) Mild uptake in the intracardiac portion of the electrode in the AC image (left and center, red arrow) without ^{18}F-FDG uptake in NAC image (right, black arrow) must be interpreted as an overcorrection artifact. *PI*, pocket infection.

both the lead and the pocket had a positive culture for the same microorganism, the existence of a lead vegetation in the context of positive blood cultures was also considered a major criterion for CIED-IE,[11] as well as the presence of pulmonary embolisms.

In most preceding studies, the diagnostic yield of PET/CT was determined for CIED infections as a

Table 7. SUV_{max} and SUV_{ratio} values according to the final diagnosis

	No CIED infection (n = 36)	Pocket infection (n = 14)	CIED-IE (n = 13)	*P* (no infection vs pocket infection)	*P* (no infection vs CIED-IE)
Pocket SUV_{max}	3.7 (3.0-4.9)	5.5 (3.1-7.4)	2.9 (2.8-3.4)	.333	.219
Pocket SUV_{ratio}	1.3 (1.0-1.9)	2.1 (1.1-3.0)	1.2 (1.0-1.7)	.418	.539
Lead (extracardiac) SUV_{max}	1.9 (1.6-2.3)	4.6 (3.2-5.7)	3.2 (2.9-3.8)	**< .001**	**.005**
Lead (extracardiac) SUV_{ratio}	0.9 (0.7-0.9)	2.0 (1.5-2.3)	1.5 (1.0-1.8)	**< .001**	**.047**
Lead (intracardiac) SUV_{max}	2.7 (2.4-3.5)	3.3 (2.8-5.1)	3.0 (1.3-3.7)	.173	.596
Lead (intracardiac) SUV_{ratio}	1.2 (1.1-1.4)	1.4 (1.2-2.1)	1.2 (0-1.9)	.209	.909

Values are median and interquartile range. Bold values are significant
CIED, cardiac implantable electronic device; *IE*, infective endocarditis; *PI*, pocket infection; *SUV_{max}*, maximum standardized uptake value; *SUV_{ratio}*, prosthetic material-to-background standardized uptake value ratio

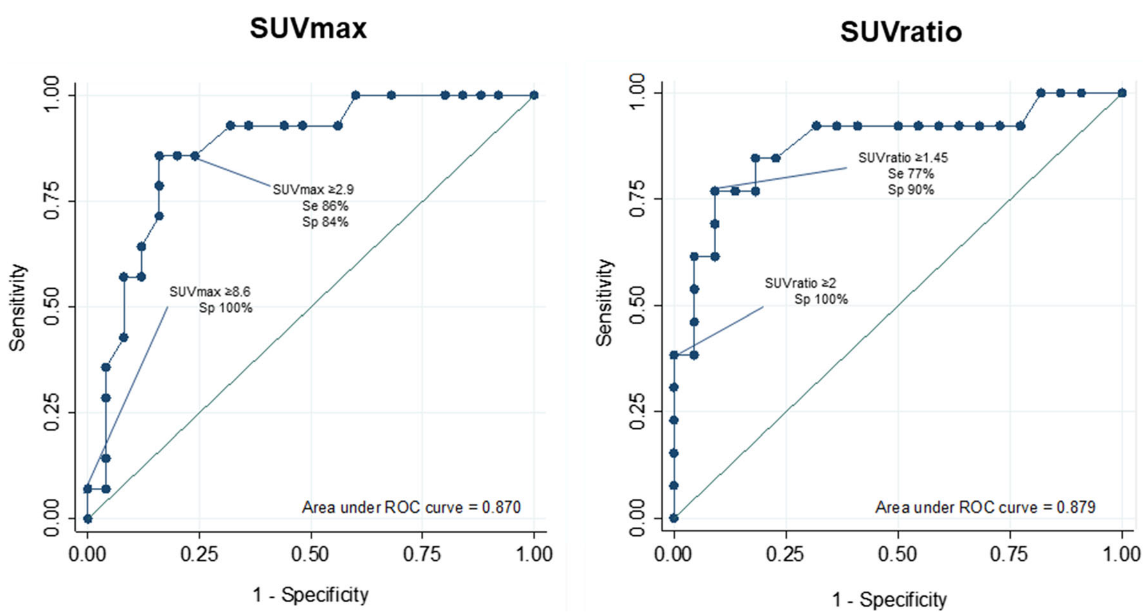

Figure 6. Receiver-operator characteristic curves for maximum standardized uptake value (SUV_{max}) and material-to-background standardized uptake value ratio (SUV_{ratio}) for extracardiac lead uptake in cardiac electronic implantable device PI. Cut-off points with the best sensitivity-specificity relationship, and with 100% specificity to confirm infection are shown. *AUC*, area under the ROC curve; *CIED*, cardiac electronic implantable device; *PI*, pocket infection; *Se*, sensitivity; *Sp*, specificity; *SUV_{max}*, maximum standardized uptake value; *SUV_{ratio}*, prosthetic material-to-background standardized uptake value ratio.

whole,[4,5,15] obtaining good values of sensitivity (83%-85%) and even higher specificity (95%-100%). Conversely, the few studies that focused on the diagnostic role of PET/CT in CIED-IE,[6,7] considering lead radionuclide uptake for the diagnosis, reported lower values of sensitivity and specificity (30.8%-63% and 62.5%-86%, respectively). In our cohort, using this same diagnostic criterion, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy for CIED-IE diagnosis were 53.8%, 72.0%, 33.3%, 85.7% and 68.3%, respectively. However, provided that radionuclide uptake at the extravascular portion of the lead is often an extension of pocket area inflammation, we also evaluated the yield of this imaging technique only taking into account the presence of ^{18}F-FDG uptake in the intracardiac portion of the lead. In this situation, we obtained even lower sensitivity values (38.5%) with a marked increase in specificity (98.0%), positive predictive value (83.3%) and accuracy (85.7%). This low sensitivity is consistent with that obtained in the recently published Euro-Endo Registry (16.2%).[20] The high negative predictive value (86.0%) despite the low sensitivity of PET/CT must be cautiously analyzed and has to be interpreted considering the high prevalence of CIED-IE in our cohort of patients (20.6%). Thus, as negative likelihood ratio (0.6) indicates, diagnosis of CIED-IE cannot be excluded when PET/CT is negative. However, as it is displayed in Fagan nomogram (Figure 3), considering the prevalence of CIED-IE in our cohort, such a positive likelihood ratio (19.2) corresponds to a post-test probability of 83%, suggesting that a positive result of PET/CT is highly suspicious of CIED-IE.

Reasons explaining a low sensitivity of PET/CT in the diagnosis of CIED-IE have been considered. Some authors have pointed out that an inadequate patient preparation might partly explain these results.[6,7] However, in our cohort, all patients systematically underwent dietary measures to ensure an adequate myocardial suppression, which was achieved in 92% of patients, without influencing the proportion of cases with a false negative PET/CT study. In any case, sensitivity and specificity of PET/CT in our cohort was similar to that reported in studies which did not use such a very strict cardiac preparation.

Other factors that may influence the diagnostic yield of PET/CT in CIED-IE include administration of antibiotic therapy prior to imaging and vegetation size due to PET/CT limited special resolution.

Although it is commonly accepted that antibiotics can diminish ^{18}F-FDG uptake,[6,7,21,22] several studies have reported that antibiotic therapy did not significantly affect the rate of false negative studies.[9,10,17] The results observed in our cohort support this hypothesis, as we did not find significant differences in the median time of antibiotic therapy between false negative and true positive studies (Table 5). Conversely, Bensimhon et al found that false negative studies in their series occurred in those patients who had received antibiotic therapy for a longer period of time (20 days in false negative cases vs 3.2 days in true positive cases).[15] Similar results have been more recently reported by Diemberger et al.[22] Thus, some authors have proposed to cautiously interpret the results of PET/CT if antibiotic therapy is longer than a week,[15] and others have even suggested establishing an adequate period of time for performing the PET/CT study after withdrawal of antibiotics.[6]

More important than the time of antibiotic therapy may be the level of systemic inflammatory activity, as it has been described in a recent work of PET/CT in patients with prosthetic valve IE, in which the percentage of false negative studies was higher in patients with low inflammatory activity.[23] However, in our work we did not find that leukocyte count or C-reactive protein (CRP) levels significantly differed between true positive and false negative cases.

The limited spatial resolution of PET/CT and the potential role of partial volume effect might be of particular importance to explain the low sensitivity of this technique in CIED-IE. In our cohort, no significant differences were observed regarding vegetation size when comparing false negative and true positive PET/CT studies. To deal with this technical limitation, Leccisotti et al proposed the use of delayed acquisition, 3 hours after ^{18}F-FDG injection, which would permit the clearance of blood pool activity and provide a better target-to-background contrast.[16] In their study, the diagnostic accuracy of PET/CT significantly improved, from 51% to 70%, due to an increase in sensitivity, without modifying specificity.[16]

According to ESC guidelines, radiolabelled leukocyte single-photon emission tomography and computed tomography (WBC-SPECT/CT) may be considered an additive tool in the diagnosis of prosthetic valve IE.[3] However, data on WBC-SPECT/CT usefulness in the assessment of CIED-IE is currently limited to a few recently published studies, providing high diagnostic accuracy due to very high specificity.[24,25] This imaging technique, compared to PET/CT, has a substantially longer acquisition protocol (24 vs 2 hours), less special resolution and involves manipulation of blood products for labelling.

Semi-quantitative Analysis

Most studies had used both visual analysis and semi-quantitative assessment of ^{18}F-FDG uptake.[2,5,6,15–17] However, the methods used for the semi-quantitative analysis are heterogeneous among different studies, as some investigations evaluated the SUV_{max}, whereas others measured the ratio between the standardized uptake value of the target region and the background (SUV_{ratio}).

In most studies, SUV_{max} did not adequately discriminate infected and non-infected leads,[2,6,15] or was of no additional value compared to visual analysis.[17] As pointed out by Bensimhon et al, the individual variability in ^{18}F-FDG circulating and uptake probably led to similar values of SUV_{max} in controls and infected patients.[15]

Interestingly, SUV_{ratio} or target-to-background ratio provided better diagnostic accuracy in other studies.[5,16] In our cohort of patients, both SUV_{max} and SUV_{ratio} extracardiac lead values were significantly higher in patients with CIED PI and CIED-IE, compared to patients without CIED infection, but pocket and intracardiac values did not adequately discriminated CIED infection.

Regardless, further studies are necessary to standardize the semi-quantitative analysis and define precise cut-off values in the setting of suspected CIED-IE.

Pulmonary Embolisms in CIED-IE

Pulmonary embolism, a frequent complication of patients with CIED-IE, represents a minor diagnostic Duke criterion of IE, and can help in achieving the diagnosis. Nevertheless, this complication has been specifically addressed in a scant number of series of CIED-IE studied by PET/CT.[2,7,17,25] In our cohort, PET/CT documented pulmonary embolisms in 2 out of 13 patients and in both cases pathological FDG uptake in the intracardiac portion of the lead was detected. Thus, this condition should be actively sought by PET/CT in any patient with the suspicion of CIED-IE.

Incorporating PET/CT in the Diagnostic Work-Up of Suspected CIED-IE: Clinical Implications

Several studies have proposed algorithms for the evaluation and management of patients with CIED, incorporating PET/CT results. Sarrazin et al, Tlili et al and Juneau et al advocate that in patients with suspected CIED infection not confirmed by conventional work-up (echocardiography and blood cultures) PET/CT should be performed, and if negative, physicians should look for an alternative cause of infection.[4,5,21] In the same line of reasoning, Ploux et al suggested that in patients with CIED and fever of unknown origin despite TEE, a positive PET/CT should be followed by device extraction, whereas in cases with negative PET/CT, CIED should not be removed, performing close clinical follow-up.[14] Sarrazin et al went one step further and concluded that in cases of suspected CIED with a positive TEE but negative blood cultures, a negative PET/CT would rule out the presence of active infection.[5] Considering the results of our study and taking into account that in most cases of suspected CIED infections antibiotic therapy is initiated before PET/CT is performed, we believe that this last proposal is particularly reckless and should not be applied, especially if the clinical presentation favors the presence of a systemic infection.

Limitations

The present study has several limitations. First, it is a single-center, observational study in which referral bias may have affected results. The small number of patients of our study does not allow the formulation of definitive conclusions. The Endocarditis Team was not blind to PET/CT results, as they provided relevant data for patient´s management. The absence of a reference gold standard for CIED-IE is a common limitation to all studies on this subject, which hinders the evaluation of new diagnostic techniques, such as PET/CT, in the field of IE. Regarding our applied gold standard, the time from PET/CT to device removal, and the time from antibiotic treatment to device removal might have influenced the results of the device cultures. In addition, the presence of CIED infection cannot be irrefutably ruled out in patients treated with antibiotics for left-sided IE. Finally, heterogeneity in preparation of PET/CT cannot be conclusively excluded.

New Knowledge Gained

The main novelties of our manuscript are the following:

- In comparison with most of previous studies on the matter, all patients in our cohort were prospectively collected. They were all evaluated by the Endocarditis team, and although relatively small, it comprises the largest prospective cohort of patients with suspected CIED infections to date in which the diagnostic yield of PET/CT has been analyzed.
- Special emphasis was placed on differentiating between pocket and lead infection. Moreover, very precise definitions for CIED-IE and PI were applied in our study, taking into account possible misdiagnosis related to contamination of the lead due the device extraction technique.
- In comparison with previous published studies, accuracy of ^{18}F-FDG PET/CT in CIED-IE was evaluated for both the intracardiac and the extracardiac portions of the lead, provided that radionuclide uptake at the extracardiac segment is often an extension of pocket area inflammation. Considering only the intracardiac portion of the lead, we obtained even lower sensitivity values (38.5%) with a marked increase in specificity (98.0%), positive predictive value (83.3%) and accuracy (85.7%). Besides, reasons previously reported to explain the low sensitivity of PET/CT in the diagnosis of CIED-IE have been evaluated.
- As negative likelihood ratio (0.6) indicates, diagnosis of CIED-IE cannot be excluded when PET/CT is negative. However, according to the prevalence of CIED-IE in our cohort, such a high positive likelihood ratio (19.2) corresponds to a post-test probability of 83%, suggesting that a positive result of PET/CT is highly suspicious of CIED-IE.

CONCLUSIONS

In patients with suspected CIED infection, the yield of ^{18}F-FDG PET/CT varies depending on the location of the infection. In PI, PET/CT had fair enough sensitivity and very good specificity. Conversely, in CIED-IE, the technique had very high specificity but poor sensitivity. In this last scenario, negative studies should be interpreted with caution if the suspicion of CIED-IE is high.

Disclosures

Adrián Jerónimo, Carmen Olmos, Isidre Vilacosta, Aida Ortega-Candil, Cristina Rodríguez-Rey, María Jesús Pérez-Castejón, Cristina Fernández-Pérez, Carlos Nicolás Pérez-García, Daniel García-Arribas, Carlos Ferrera, and José Luis Carreras state that they have no conflicts of interest to declare.

References

1. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, et al. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: Increased valvular ^{18}F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol 2013;61:2374-84.
2. Pizzi MN, Roque A, Fernández-Hidalgo N, Cuéllar-Calabria H, Ferreira-González I, Gonzàlez-Alujas MT, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with ^{18}F-fluordeoxyglucose positron emission tomography/computed tomography angiography. Initial results at an infective endocarditis referral center. Circulation 2015;132:1113-26.
3. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075-128.
4. Tlili G, Amraoui S, Mesguich C, Rivière A, Bordachar P, Hindié E, et al. High performances of $^{(18)}$F-fluorodeoxyglucose PET–CT in cardiac implantable device infections: A study of 40 patients. J Nucl Cardiol 2015;22:787-98.
5. Sarrazin JF, Philippon F, Tessier M, Guimond J, Molin F, Champagne J, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol 2012;59:1616-25.
6. Cautela J, Alessandrini S, Cammilleri S, Giorgi R, Richet H, Casalta JP, et al. Diagnostic yield of FDG positron-emission tomography/computed tomography in patients with CEID infection: A pilot study. Europace 2013;15:252-7.
7. Graziosi M, Nanni C, Lorenzini M, Diemberger I, Bonfiglioli R, Pasguale F, et al. Role of ^{18}F-FDG PET/CT in the diagnosis of infective endocarditis in patients with an implanted cardiac device: A prospective study. Eur J Nucl Med Mol Imaging 2014;41:1617-23.
8. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ, et al. EANM/SNMMI guideline for ^{18}F-FDG use in inflammation and infection. J Nucl Med 2013;54:647-58.
9. Jiménez-Ballvé A, Pérez-Castejón MJ, Delgado-Bolton RC, Delgado-Bolton RC, Sánchez-Enrique C, Vilacosta I, et al. Assessment of the diagnostic accuracy of $^{(18)}$F-FDG PET/CT in prosthetic infective endocarditis and cardiac implantable electronic device infection: Comparison of different interpretation criteria. Eur J Nucl Med Mol Imaging 2016;43:2401-12.
10. Erba PA, Lancellotti P, Vilacosta I, Gaemperli O, Rouzet F, Hacker M, et al. Recommendations on nuclear and multimodality imaging in IE and CIED infections. Eur J Nucl Med Mol Imaging 2018;45:1795-815.
11. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. Mayo Clin Proc 2008;83:46-53.
12. Uslan DZ, Sohail MR, St Sauver JL, Friedman PA, Hayes DL, Stoner SM, et al. Permanent pacemaker and implantable cardioverter defibrillator infection. Arch Intern Med 2007;167:669-75.
13. Downey BC, Juselius WE, Pandian NG, Estes NA 3rd, Link MS. Incidence and significance of pacemaker and implantable cardioverter-defibrillator lead masses discovered during transesophageal echocardiography. Pacing Clin Electrophysiol 2011;34:679-83.
14. Ploux S, Riviere A, Amraoui S, Whinnett Z, Barandon L, Lafitte S, et al. Positron emission tomography in patients with suspected pacing system infections may play a critical role in difficult cases. Heart Rhythm 2011;8:1478-81.
15. Bensimhon L, Lavergne T, Hugonnet F, Mainardi JL, Latremouille C, Maunoury C, et al. Whole body [$^{(18)}$ F]fluorodeoxyglucose positron emission tomography imaging for the diagnosis of pacemaker or implantable cardioverter defibrillator infection: A preliminary prospective study. Clin Microbiol Infect 2011;17:836-44.
16. Leccisotti L, Perna F, Lago M, Leo M, Sterfanelli A, Calcagni ML, et al. Cardiovascular implantable electronic device infection: Delayed vs standard FDG PET–CT imaging. J Nucl Cardiol 2014;21:622-32.
17. Granados U, Fuster D, Pericas JM, Llopis JL, Ninot S, Quintana E, et al. Diagnostic accuracy of ^{18}F-FDG PET/CT in infective endocarditis and implantable cardiac electronic device infection: A cross-sectional study. J Nucl Med 2016;57:1726-32.
18. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections—Endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Europace 2020;22:515-49.
19. Sandoe JA, Barlow G, Chambers JB, Gammage M, Guleri A, Howard P, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic devices infection. Report of a Joint Working Party Project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). J Antimicrob Chemother 2015;70:325-59.
20. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European Infective Endocarditis) Registry: A prospective cohort study. Eur Heart J 2019;40:3222-32.

21. Juneau D, Golfam M, Hazra S, Zuckier LS, Garas S, Redpath C, et al. Positron emission tomography and single-photon emission computed tomography imaging in the diagnosis of cardiac implantable electronic device infection: A systematic review and meta-analysis. Circ Cardiovasc Imaging 2017;10:1-11.
22. Diemberger I, Bonfiglioli R, Martignani C, Graziosi M, Biffi M, Lorenzett S, et al. Contribution of PET imaging to mortality risk stratification in candidates to lead extraction for pacemaker or defibrillator infection: A prospective single center study. Eur J Nucl Med Mol Imaging 2019;46:194-205.
23. Swart LE, Gomes A, Scholtens AM, Sinha B, Tanis W, Lam MGEH, et al. Improving the diagnostic performance of ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography in prosthetic heart valve endocarditis. Circulation 2018;138:1412-27.
24. Holcman K, Maleka B, Rubis P, Zabek A, Szot W, Boczar K, et al. The role of ^{99m}Tc-HMPAO-labelled white blood cell scintigraphy in the diagnosis of cardiac device-related infective endocarditis. Eur Heart J Cardiovasc Imaging. 2019. https://doi.org/10.1093/ehjci/jez257.
25. Calais J, Touati A, Grall N, Laouénan C, Benali K, Mahida B, et al. Diagnostic impact of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and white blood cell SPECT/computed tomography in patients with suspected cardiac implantable electronic device chronic infection. Circ Cardiovasc Imaging. 2019;12:e007188.