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DIAGNOSTIC ACCURACY OF ^{18}F-FDG PET/CT IN INFECTIVE ENDOCARDITIS AND IMPLANTABLE CARDIAC ELECTRONIC DEVICE INFECTION: A CROSS-SECTIONAL STUDY

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ABSTRACT

Early diagnosis of infective endocarditis (IE) is based on the yielding of blood cultures and echocardiographic findings. However, they have limitations and sometimes the diagnosis is inconclusive, particularly in patients with prosthetic valves (PV) and implantable cardiac electronic devices (ICED). The primary aim of this study was to evaluate the diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with suspected IE an ICED infection. **Methods:** A prospective study with 80 consecutive patients with suspected IE and ICED infection (65 men and 15 women with a mean age of 68±13 years old) between June 2013 and May 2015 was performed in our hospital. The inclusion criteria was clinically suspected IE and ICED infection at the following locations: native valve (NV) (n=21), PV (n=29) or ICED (n=30) [(automatic implantable defibrillator (n=11) or pacemaker (n=19)]. Whole-body ^{18}F-FDG PET/CT with a myocardial uptake suppression protocol with unfractionated heparin was performed in all patients. The final diagnosis of infection was established by the IE study Group according to the clinical, echocardiographic and microbiological findings. **Results:** A final diagnosis of infection was confirmed in 31 patients: NV (n=6), PV (n=12) and ICED (n=13). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for ^{18}F-FDG PET/CT was 82%, 96%, 94% and 87%, respectively. ^{18}F-FDG PET/CT was false negative in all cases with infected NV. ^{18}F-FDG PET/CT was able to reclassify 63/70 (90%) patients initially classified as possible IE by modified Duke criteria. In 18/70 cases ^{18}F-FDG PET/CT changed possible to definite IE (26%) and in 45/70 cases changed possible to rejected IE (64%). Additionally, ^{18}F-FDG PET/CT identified 8 cases of septic embolism and 3 colorectal cancer in patients with final diagnosis of IE. **Conclusion:** ^{18}F-FDG PET/CT proved to be a useful diagnostic tool in suspected IE and ICED infection and should be included in the diagnostic algorithm for early diagnosis. ^{18}F-FDG PET/CT is not useful in the diagnosis of IE in NV, but should be also considered in the initial assessment of this complex scenario to rule out extracardiac complications and possible neoplasms.

Keywords: Infective endocarditis, implantable cardiac electronic devices, prosthetic valve, ^{18}F-FDG-PET/CT, septic embolisms.

INTRODUCTION

Infective endocarditis (IE) entails a high risk of mortality and severe complications (1). Besides, early diagnosis and detection of possible complications of IE remain a challenge in clinical practice (2). In order to improve outcomes, the diagnosis and management of IE should be shared by well-coordinated diverse specialists working altogether into a multidisciplinary team (3). Blood cultures and echocardiographic findings are still in the cornerstone in the suspicion and initial diagnosis of IE, which will be utterly confirmed or rejected according to modified Duke criteria (4). However, the diagnostic yielding of current criteria is not optimal, with a large percentage of cases remaining as “possible IE” at the end of the episode (5). This is partially due to difficulties in the interpretation of echocardiographical findings in patients harbouring intracardiac devices as are prosthetic valves (PV) and implantable cardiac electronic devices (ICED) (6).

Early detection and drainage if required of embolic complications, as well as enlarging the length of antibiotic therapy is crucial for improving immediate and late outcomes of IE, including relapses (7,8). Additionally, some microorganisms frequently causing IE such as *Bovis group streptococci* are linked to underlying neoplasms (9). The detection of a neoplasm in the context of IE might have great impact in other therapeutic decisions and their timing, as it is the performance of cardiac surgery. Therefore, prospects in the approach of IE rely on available and easy-to-perform tests that provide data on different issues at once so early measures could be applied.

18F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an emerging image technique which has proven useful in the diagnosis of a variety of infectious diseases (10,11). Its utility is due to the ability of FDG to actively incorporate into activated leukocytes, macrophages and CD4 + T cells present at the sites of infection (12,13). Recent studies have reported encouraging results for ^{18}F-FDG PET/CT in the diagnosis of IE and ICED infection (14-16), as well as to detect extracardiac complications (17,18). In the most recent guidelines of the European Society of Cardiology (ESC 2015), ^{18}F-FDG PET/CT has been included as a major criterion of prosthetic valve endocarditis (PVE) diagnosis and also in the diagnostic algorithm for the detection of embolic events both native valve IE (NVE) and PVE (7).

The primary aim of this study was to evaluate the diagnostic accuracy of ^{18}F-FDG PET/CT in patients with suspected NVE, PVE, ICED IE and others ICED-associated infections. The secondary aims were to evaluate the interobserver agreement and the added value of quantification using standardize uptake value (SUV) in diagnosis of infection.

MATERIALS AND METHODS

Patients and Design

Retrospective analysis of prospectively collected data from 80 consecutive patients (65 men and 15 women with a mean age of 68±13 years old) with suspected IE and ICED infection attended from June 2013 to May 2015, in our hospital. Since 1979, all patients with IE attended at the Hospital Clinic of Barcelona have been managed by a multidisciplinary group that joined in a weekly basis (19). We included patients with clear suspicion of native or prosthetic valve IE and ICED IE or infection, at least accomplishing Duke modified criteria to be initially considered as possible cases. After the diagnostic process, including ^{18}F-FDG PET/CT and other tests, cases were classified according to modified Duke criteria (4) in rejected, definite or possible. In the case of ICED, and due to the common management in all cases (removal of the device), we used the definitions provided by the last BSAC guidelines (20) for those cases not presenting vegetations (i.e. pocket infection and ICED lead infection). The final diagnosis of infection was established by the multidisciplinary working group according to the clinical, echocardiographic and microbiological findings. ^{18}F-FDG PET/CT results were communicated to referring clinicians shortly after the test was done. Thus, ^{18}F-FDG PET/CT was used as a diagnostic tool also, being a major criterion in the case of PVE, as recognised by last ESC Guidelines (7) In the case of ICED, ^{18}F-FDG PET/CT was used in the cases in which the suspicion was high but none of the classic findings of ICED-associated infection was present (local inflammation of the generator pocket, bacteremia or vegetations). Definitions of variables related to IE collected in the clinical sheet of all patients The following suspected episodes were included NVE (n=21), PVE (n=29) and ICED IE or ICED infection (n=30) [(automatic implantable defibrillator (n=11) or pacemaker (n=19). All the patients were under antibiotic theraphy. The baseline characteristics of the patients are shown in Table 1. The exclusion criteria included severe hemodynamic instability and indications for emergent surgery. All patients surviving the initial admission had at least a follow up of 6 months.

The institutional review board approved this study and all subjects signed a written informed consent.

PET/CT

Whole-body scans were performed using a hybrid PET/CT scanner (SIEMENS Biograph mCT 64S) A myocardial uptake suppression protocol was followed with a fasting period for at least 12 hours and intravenous administration of 50 IU/kg of unfractionated heparin 15 minutes prior to the injection of 4.0 MBq/Kg of ^{18}F-FDG. Blood glucose levels were required to be less than 150 mg/dl during a period of approximately 60 minutes before the administration of the ^{18}F-FDG; during acquisitions, patients were in supine position with their arms raised above the head. Whole-body PET data were acquired in three-dimensional mode and for 3 minutes per bed position.

Image Interpretation

Images were interpreted separately by two independent observers (two nuclear medicine specialists trained on infection and ^{18}F-FDG PET/CT who were blinded to the clinical results. Disagreements were settled by consensus with a third nuclear medicine specialist. The criterion for infection was visual and considered positive when focal or heterogeneous increase in ^{18}F-FDG activity related to the PV, NV or ICED were identified in the attenuation corrected and uncorrected images. A semi-quantitative analysis was made using the maximum SUV (SUVmax) in the area of suspected infection. The SUVmean was obtained in the blood pool (superior cava vein) and in the liver to establish SUV ratios. The SUVratio was calculated by dividing the SUVmax of the area of interest by the blood pool SUVmean (SUVmax ratio 1) and the liver SUVmean (SUVmax ratio 2).

Myocardial uptake suppression was classified in three categories as: complete inhibition uptake (less or equal to liver uptake); partial inhibition (focally above to liver) and non-inhibition (diffusely superior to liver uptake). Receiver operating characteristic (ROC) curves with two different thresholds regarding total optimisation and sensitivity optimisation for SUVmax and SUVmax ratios have been obtained.

Statistical Analysis

The analyses were performed using SPSS, version 22.0 (SPSS Inc.). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. Inter-agreement kappa was obtained. ROC curves and total and sensitivity optimization thresholds have been calculated. P values <0.05 were considered statistically significant. A Mann-Whitney U test for continuous variables and a Fisher's exact test for nominal variables were used to assess differences between groups with p-values <0.05 considered statistically significant.

RESULTS

A final diagnosis of infection was established in 31 patients: NVE (n= 6), PVE (n= 12) [biological valve (n=5) or mechanical valve (n=7)], ICED IE (n= 8) and ICED pocket or lead infection (n= 5) [automatic implantable defibrillator (n=5) or pacemaker (n=8)] (Figs. 1 and 2A). Forty-seven patients were rejected and 2 patients remained as "possible". In 28 out 31 episodes causing microorganism was identified, being *Staphylococcus aureus* (n= 8) and coagulase- negative staphylococci (n= 6) the most frequently isolated (Table 2). Sensitivity, specificity, PPV and NPV for ^{18}F-FDG PET/CT were 82%, 96%, 94% and 87%, respectively. When NV are excluded from the analysis, these values change to 96%, 94%, 93% and 97%, respectively.

In our series, ^{18}F-FDG PET/CT was able to reclassify 63/70 cases (90%) initially classified as possible IE by modified Duke criteria. In 18/70 cases ^{18}F-FDG PET/CT changed possible to definite IE (26%) and in 45/70 cases changed possible to rejected IE (64%) (Table 3). Additionally, ^{18}F-FDG PET/CT identified 8 cases of septic embolism (26%) in patients with a final diagnosis of IE (pulmonary, splenic and vertebral in 4, 2 and 2 cases, respectively) (Fig. 2B): and 3 cases of colorectal cancer in patients with IE caused by *Streptococcus bovis* (n= 2) and *Enterococcus faecalis* (n= 1).

Among those patients with suspected IE or ICED infection whose diagnosis was eventually rejected, ^{18}F-FDG PET/CT findings were: pneumonia (n=4), hip septic arthritis (n= 2), spondylodiskitis, (n= 2), sternal osteomyelitis (n= 1), vascular aortic graft infection (n= 1) and one case of lymphoma. Interestingly, ^{18}F-FDG PET/CT detected the source of infection in 7/15 patients (47%) with NV and rejected IE as final diagnosis.

^{18}F-FDG PET/CT retrieved 7 false negative results in patients with definite IE, including all 6 cases with NVE and one case of PVE. There were no significant differences on the length of antibiotic therapy prior to ^{18}F-FDG PET/CT performance between false negative and true positive results (p= 0.87). On the contrary, there were 2 ^{18}F-FDG PET/CT false positive cases with suspicion of early PVE (one month and 8 months after cardiac surgery, respectively).

The most valuable semi-quantitative score to diagnose infection was SUVmax (Table 4). However, we did not find any significant improvement using semi-quantitative scores in terms of sensitivity and specificity compared to visually analysis. Myocardial uptake inhibition was achieved in 75% of the patients (49 complete and 11 partial) Additionally, mean SUVmax in the group of patients with a complete inhibition of the myocardium and in the non-inhibited group were 3.7±1.3 and 12.3±6.1 (p<0.01), respectively (Fig. 3).. The mean SUVmax in partially inhibited patients was 5.9±1.4 (p= ns).

There were 74 ^{18}F-FDG PET/CT concordant results out of the 80 included cases corresponding to a 92% of agreement. The Kappa statistics value to measure inter-rater agreement was 0.81 (p<0.01).

DISCUSSION

In spite of accurate multidisciplinar approach, IE and ICED infections remains still underdiagnosed. As a consequence, the equivocal timing of empirical treatment instauration and consideration for cardiac surgery leads to poor prognosis in a considerable proportion of patients. The presence of PV and ICED consistently decreases the sensitivity and specificity of echocardiography, to about 20% for transthoracic echocardiography and around 90% (in the hands of an experienced operators) for transesophageal echocardiography (6). Erba et al (21) have demonstrated that 99mTc-HMPAO- white blood cell labelled scintigraphy is useful to locate the source of infection in patients with sepsis of different origins. However, this technique is time-consuming and its resolution is low, even using SPECT/CT images.

Earliest studies with ^{18}F-FDG PET/CT in IE showed low sensitivities for detecting intracardiac infectious focci, which was attributed to the high myocardium physiological uptake. Inspired in viability studies, several works have developed different strategies in order to inhibit myocardial uptake In most studies, ^{18}F-FDG PET/CT was performed after long fasting (at least 12 hours) and a previous meal rich in fat and very low in carbohydrates (14). Williams et al in a series of 101 patients, showed that a very high-fat, low-carbohydrate, protein-permitted meal eaten 3-6 hours before FDG injection is useful, being the average SUVmax significantly lower for the very high-fat, low-carbohydrate, protein-permitted meal group compared with that of the fasting group (8.8 ± 5.7 and 3.9 ± 3.6, respectively) (22), In our series, we found similar scores of mean SUVmax in the group of patients with a complete inhibition of the myocardium using heparin of 3.7±1.3. However, we could only consider a complete myocardial uptake inhibition in 49 patients (61%) and partial inhibition in 11 patients (14%), so it would be of interest to compare both methods to define if myocardial uptake suppression could be improved. The most accurate procedure described in the literature includes prolonged fasting with low carbohydrate diet and heparin injection (23).

There is an increasing amount of studies from groups waging to implement ^{18}F-FDG PET/CT as an essential tool for IE and ICED infection diagnosis (14-16). Saby et al suggested that the sensitivity of the modified Duke criteria to diagnose PVE can be enhanced if ^{18}F-FDG-PET/CT results are incorporated into a comprehensive approach including clinical, microbiological and echocardiographic parameters (14). Pizzi et al found that addition of ^{18}F-FDG PET/CT as major Duke criteria at admission significantly increased diagnostic sensitivity from 52% to 90.7% with only a minor decrease in specificity, mainly due to a significant reduction in the number of possible IE cases (from 54% to 5%) (24). However, these authors included initially rejected patients by modified Duke criteria probably making less cost-effective the indication of ^{18}F-FDG PET/CT in suspected IE. Our study did not include initially rejected IE patients by modified Duke criteria showing a high specificity in all the indications where ^{18}F-FDG PET/CT was performed (including and excluding NV were 96% and 94%, respectively). Moreover, ^{18}F-FDG PET/CT allowed to reclassify the 90% of our patients initially classified as possible IE,. Pizzi et al. also recommend the use of hybrid ECG gating and contrast enhanced PET/CT but they do not find significant differences in sensitivity and specificity between contrast and non contrast enhanced PET/CT. On the other hand, contrast enhanced PET/CT represents an increase in both complexity of the procedure and dosimetry (increase of median effective radiation dose from 15.3 to 25.3 mSv) (24).

^{18}F-FDG PET/CT may have an impact in surgical management of patients with IE and simultaneous ICED and PV, due to its high NPV (97% when NVE are excluded), being helpful in selecting which device should be removed. Note that ^{18}F-FDG PET/CT also was able to detect the source of infection in 7/15 patients (47%) with NV and rejected IE.

As it is was pointed by Chen et al the myocardial uptake observed in the immediate postoperatory period may be more likely related to persistent inflammatory changes rather than an ongoing infection (25). In our series we only found 2 false positive cases, both suspicions of early PVE, in which ^{18}F-FDG PET/CT was performed one month and 8 months after surgery, respectively. However, we have not found any false positive case in the ICED group, even in the early disposed devices (<1 year since implantation).

The presence of septic emboli is crucial for the correct management of patients with IE and ICED infection. Failure to identify metastatic infection complications may lead to early interruption of therapy, thus potentially triggering relapse and an unfavourable outcome. Infectious embolisms are not uncommon as they can appear between 20%-50% of patients and can be asymptomatic and difficult to recognize (7, 17,18). We were able to identify up to 8 cases of clinically unsuspected septic embolism situated mainly in the lung and in the bone. On the other hand, ^{18}F-FDG PET/CT diagnosed 3 confirmed colorectal cancer linked to IE caused by *Streptococcus bovis and Enterococcus faecalis* (9).

Sarrazin et al studied the value of a semi-quantitative 4 grade-scale for ^{18}F-FDG uptake which failed to accurately discriminate infection in patients with ICED (16). In our series, we used SUVmax and two different SUVratios using blood pool SUVmean and the liver SUVmean, concluding that SUVmax is the most appropriate semi-quantitative parameter, with a sensitivity and specificity both superior to 90%. However, there was no additional value of using SUVmax compared to visual analysis, so semi-quantitative score should not be recommended for daily clinical practice for diagnosis of infection in these patients.

LIMITATIONS

This study has several limitations. Firstly, since results of ^{18}F-FDG PET/CT was made available to clinicians immediately after the test was carried out, subsequent treatment of the patients including decisions to perform surgery were influenced by the index test. Secondly, a complete myocardial uptake inhibition was not achieved in all patients, so our suggested preparation of prolonged fasting and heparin must be combined with a low-carbohydrate diet (23).

CONCLUSIONS

^{18}F-FDG PET-CT proved to be a useful technique and should be included in the algorithm flowchart for early diagnosis of PVE, ICED IE and ICED infection reducing the rate of misdiagnosed patients. Besides, ^{18}F-FDG PET/CT can simultaneously diagnose systemic complications as septic emboli and unsuspected neoplasms, influencing substantially the management of the patients. However, ^{18}F-FDG PET-CT was not useful in the diagnosis of NVE, although in this group of patients improves the detection of causative source of infection. In addition, the interobserver agreement was excellent and we did not find any significant improvement of quantification using SUV compared to visual analysis in diagnosis of infection in this series.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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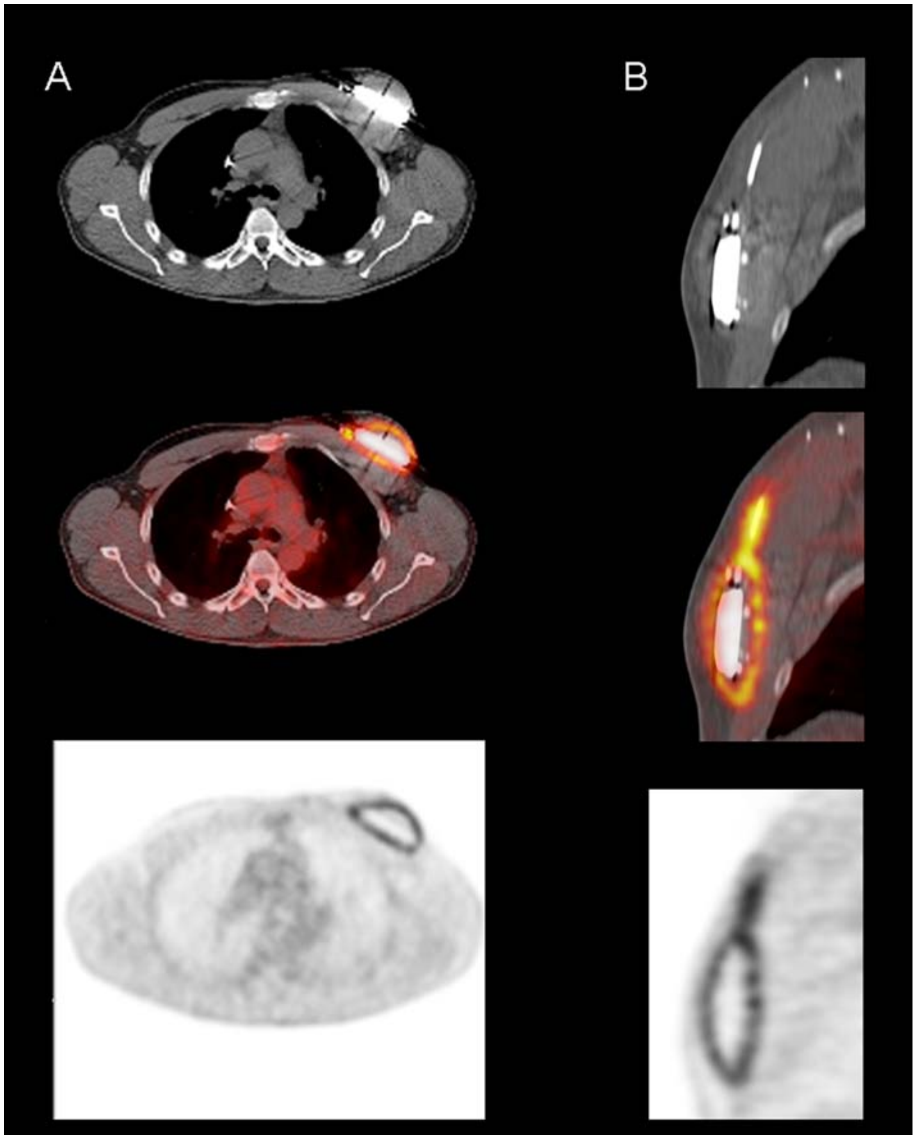

Figure 1: Pocket generator and lead infection in a patient with an automatic implantable defibrillator. Transverse (A) and sagittal (B) ^{18}F-FDG PET/CT images. The device was removed. Both generator and lead cultures were positive for *Stahpylococcus aureus*.

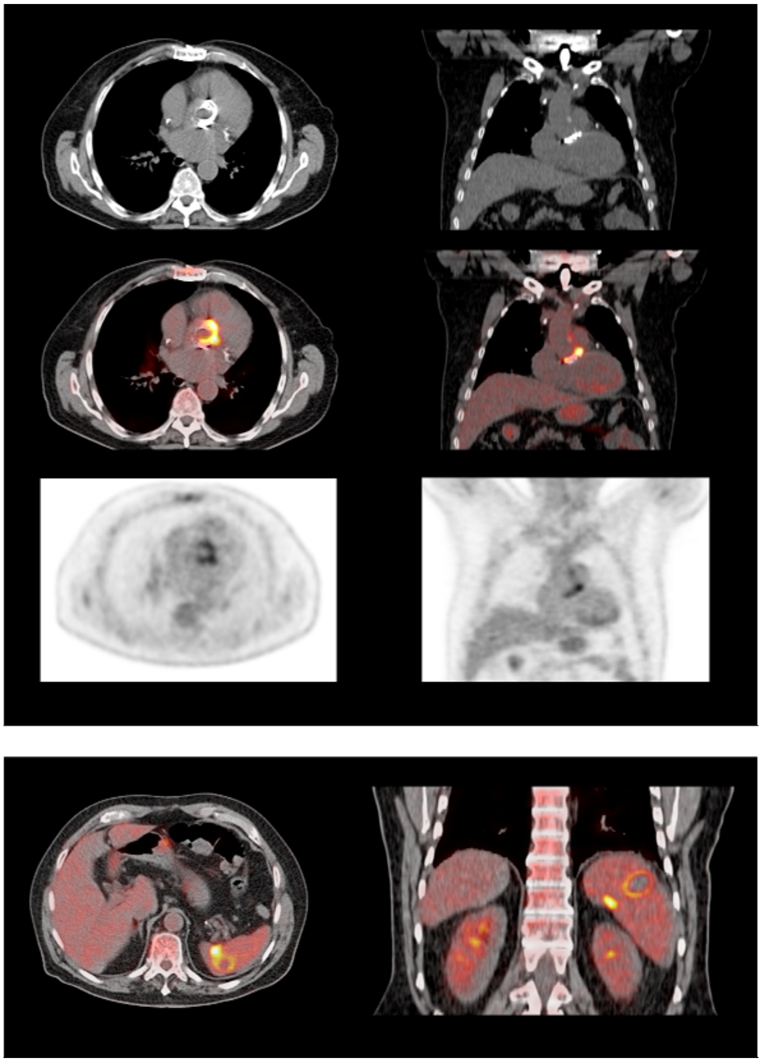

Figure 2: Transverse and coronal ^{18}F-FDG PET/CT images show an infected prosthetic aortic valve (A). The culture after valve removal was positive for *Propionebacterium acnes*. Fusion PET/CT images also demonstrate septic spleen embolisms (B).

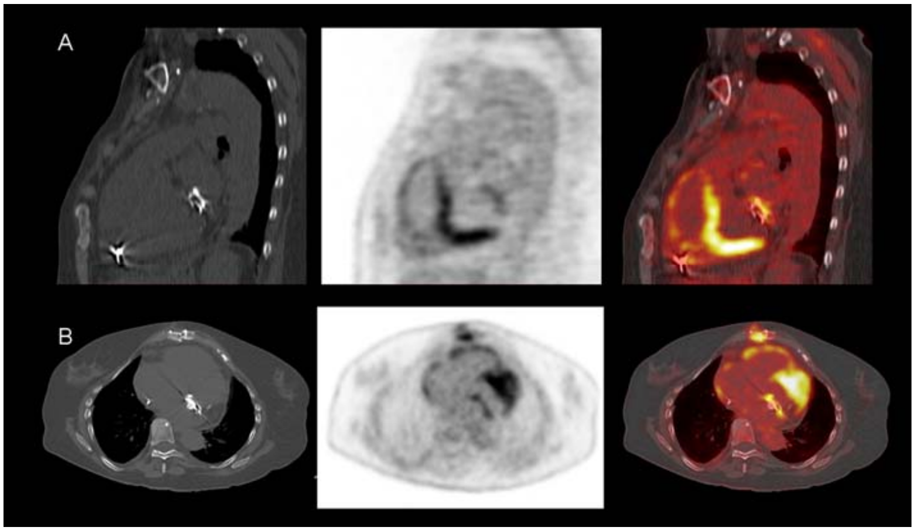

Figure 3: Sagital (A) and transverse (B) ^{18}F-FDG PET/CT images show an infected prosthetic mitral valve. The culture was positive for *Coagulase-negative Staphylococcus*. Note that the high background myocardial uptake was not cause of misdiagnosis.

TABLES

Table 1: Baseline characteristics of the study group patients.

Characteristics	**All cases (n= 80)**	**Definite IE/ICED infection (n= 10)**	**Possible IE/ICED infection (n= 70)**	**P**
Mean age (years)	68±13	71±14	68±13	0.50
Sex, n (%)				
Female	15 (19%)	2 (20%)	13 (19%)	0.94
Male	65 (81%)	8 (80%)	57 (81%)	0.94
Hypertension, n (%)	43 (54%)	5 (50%)	38 (54%)	0.81
Diabetes, n (%)	28 (35%)	3 (30%)	25 (36%)	0.71
Cardiac valve prosthesis*	33	3	30	0.44
Aortic	20	2	18	0.68
Bioprosthesic	12	0	12	0.34
Mechanical	8	2	6	0.22
Mitral	13	1	12	0.57
Bioprosthesic	4	0	4	0.90
Mechanical	9	1	8	0.92
Cardiac device*	36	3	33	0.31
Pacemarker	23	0	23	0.055
Defibrillator	13	3	10	0.19
Echocardiography, n (%)				
Transthoracic	80 (100%)	10 (100%)	70 (100%)	1
Transoesophageal	62 (77%)	9 (90%)	53 (76%)	0.32
Median time from prosthetic valve or cardiac device implantation (IQR†),months	47 (11-120)	54 (18-120)	41(11-93)	0.12
< 1 year, n (%)	25 (36%)	1 (10%)	24 (34%)	0.12
≥ 1 year, n (%)	44 (64%)	9 (90%)	35 (50%)	0.01
Days of antibiotics prior to PET/CT (IQR†)	15 (8-30)	20 (12- 30)	13 (8-25)	0.004

**The number of prosthetic valves and cardiac device do not match with the number of patients because some had >1 prosthetic valve or simultaneous PV and cardiac device.*

†IQR: interquartile range.

IE: Infective endocarditis.

ICED : Implantable cardiac electronic device.

Table 2: Main outcomes in the group of patients with final diagnosis of IE and ICED infection.

Characteristics	**N= 31**
Symptoms, n (%)	
Fever*	24 (77)
Skin signs of infection	3 (10)
Peripheral symptoms	3 (10)
Heart failure	4 (13)
Septic shock	2 (6)
Echocardiographic findings, n (%)	
Vegetations	11 (35)
Perianular complications	8 (26)
New valvular regurgitation	3 (10)
No findings	9 (29)
Causal microorganisms, n (%)	
Staphylococcus aureus	8 (26%)
CoNS	6 (19%)
VGS	4 (13%)
GNR	3 (10%)
Enterococcus faecalis	1 (3%)
Streptococcus bovis	2 (6%)
Other microorganisms	4 (13%)
Not identified	3 (10%)
Diagnostic microbiological tests, n (%)	
Blood cultures	19 (61%)
Valve or cardiac device cultures	9 (29%)
Cardiac surgery	18 (58%)
Mortality related to IE episode	2 (6%)

** Fever: temperature >37.3^{0}C.*
CoNS: coagulase-negative staphylococcus.
VGS: viridans group streptococci.
GNR: Gram-negative rods.
IE: Infective endocarditis.
ICED: Implantable cardiac devices.

Table 3: Classification according to initial diagnosis Criteria, ^{18}F-FDG PET/CT results and final diagnosis Criteria.

Classification	Initial diagnosis Criteria n (%)	^{18}F-FDG PET/CT results n (%)	Final diagnosis Criteria n (%)
PV (n= 30)			
Definite	3 (10)	13 (43)*	12 (40)
Possible	27 (90)	0 (0)	1 (3)
Rejected	0 (0)	17 (57) †	17 (57)
NV (n= 21)			
Definite	4 (19)	0 (0)	6 (29)
Possible	17 (81)	0 (0)	1 (5)
Rejected	0 (0)	21 (100) ‡	14 (66)
CIED (n= 29)			
Definite	3 (10)	13 (45)	13 (45)
Possible	26 (90)	0 (0)	0 (0)
Rejected	0 (0)	16 (55)	16 (55)
TOTAL (n= 80)			
Definite	10 (12)	26 (32)	31 (39)
Possible	70 (88)	0 (0)	2 (5)
Rejected	0 (0)	54 (68)	47 (56)

**Two false positive cases.*
†One false negative case.
‡Six false negative cases.
PV: Prosthetic valve.
NV: Native valve.
ICED: Implantable cardiac electronic devices.

<u>Table 4:</u> Optimisation of SUVmax and SUVmax ratios through ROC curves to establish the most appropriate threshold to diagnose IE/ICED infection.

Total optimisation	**Threshold**	**Sensitivity, % (**95% CI**)**	**Specificity,% (**95% CI**)**
SUVmax	3.485	91.3 (82.2-96,7)	93.7 (85.3-98.1)
SUVratio1*	2.388	87.0 (80.0-93-8)	91.7 (82.7-96.9)
SUVratio2†	1.373	91.3 (82.2-96,7)	81.2 (70.2-89.4)
Sensitivity optimisation			
SUVmax	2.105	95.7 (88.0-99.1)	60.4 (48.1-71.8)
SUVratio1*	1.459	95.7 (88.0-99.1)	64.6 (52.3-75.5)
SUVratio2†	1.099	95.7 (88.0-99.1)	64.6 (52.3-75.5)

**SUVmax ratio 1= SUVmax /blood pool SUVmean.*
†SUVmax ratio 2= SUVmax/liver SUVmean.
IE: Infective endocarditis.
ICED: Implantable cardiac electronic devices.