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Positron Emission Tomography/Computed Tomography for Diagnosis of Prosthetic Valve Endocarditis

Increased Valvular ^{18}F-Fluorodeoxyglucose Uptake as a Novel Major Criterion

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Objectives This study sought to determine the value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for diagnosing prosthetic valve endocarditis (PVE).

Background The diagnosis of PVE remains challenging. In PVE cases, initial echocardiography is normal or inconclusive in almost 30%, leading to a decreased diagnostic accuracy for the modified Duke criteria.

Methods We prospectively studied 72 consecutive patients suspected of having PVE. All of the patients were subjected to clinical, microbiological, and echocardiographic evaluation. Cardiac PET/CT was performed at admission. The final diagnosis was defined according to the clinical and/or pathological modified Duke criteria determined during a 3-month follow-up.

Results Thirty-six patients (50%) exhibited abnormal FDG uptake around the site of the prosthetic valve. The sensitivity, specificity, positive predictive value, negative predictive value, and global accuracy were as follows (95% confidence interval): 73% (54% to 87%), 80% (56% to 93%), 85% (64% to 95%), 67% (45% to 84%), and 76% (63% to 86%), respectively. Adding abnormal FDG uptake around the prosthetic valve as a new major criterion significantly increased the sensitivity of the modified Duke criteria at admission (70% [52% to 83%] vs. 97% [83% to 99%], $p = 0.008$). This result was due to a significant reduction ($p < 0.0001$) in the number of *possible* PVE cases from 40 (56%) to 23 (32%).

Conclusions The use of ^{18}F-FDG PET/CT was helpful for diagnosing PVE. The results of this study support the addition of abnormal FDG uptake as a novel major criterion for PVE. (J Am Coll Cardiol 2013;61:2374–82) © 2013 by the American College of Cardiology Foundation

Prosthetic valve infective endocarditis (PVE) remains a diagnostic challenge (1). The poor prognosis of this disease is associated, in particular, with deficiencies in identifying prosthetic and periprosthetic damage via echocardiography, which can lead to a delay in the application of antibiotic and surgical therapies (2,3).

Currently, the modified Duke criteria are considered to be the gold standard for diagnosing infective endocarditis. Based on clinical, echocardiographic, microbiological, and pathological findings, these criteria provide a diagnostic probability, classified as *definite*, *possible*, or *rejected* endocarditis (4). This classification has a sensitivity of approximately 80% when the criteria are evaluated at the end of patient follow-up in epidemiological studies (2,5). However, in clinical practice, the modified Duke criteria show a lower diagnostic accuracy for early diagnosis, especially in the case of PVE, for which echocardiography is normal or inconclusive in almost 30% of cases (6,7).

Recently, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been

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employed to identify inflammatory and infectious processes (8). Thus, several studies have demonstrated the role of PET/CT in detecting vascular prosthesis (9–11) and implantable pacemaker/defibrillator infections (12–14). Moreover, some case reports have suggested a possible role for this technique in diagnosing PVE (15–18), but no study has addressed this issue to date.

Therefore, we aimed to assess the diagnostic value of PET/CT in PVE and to determine whether the addition of abnormal FDG uptake as a major diagnostic criterion would improve the early sensitivity of the Duke classification upon the admission of patients with suspected PVE.

Methods

Patients. From January 2011 to June 2012, all consecutive adults admitted to the Department of Cardiology at Timone Hospital (Marseille, France) with a suspected diagnosis of PVE were prospectively eligible for entry to the study. In patients with a prosthetic valve, endocarditis was suspected in the presence of at least 1 of the following criteria: 1) unexplained persistent or recurrent fever >38°C; 2) unexplained increase in serum C-reactive protein (CRP) level >10 mg/l; 3) positive blood cultures, independent of the echocardiographic analysis results; 4) positive serological testing for *Coxiella burnetii*, *Bartonella spp.*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Aspergillus spp.*, or *Tropheryma whipplei*; and 5) a mass or a new partial prosthetic valve dehiscence observed using echocardiography. The patient exclusion criteria were pregnancy, inability to lie flat, need for urgent cardiac surgery, hemodynamic instability, cardiac surgery <1 month ago, and blood glucose level >1.8 g/l. All of the patients had clinical, microbiological, and echocardiographic evaluations and PET/CT. Patients with poor PET/CT image quality were also excluded.

Written informed consent was obtained from all of the participating patients using an approved protocol, which was required by the institutional review board.

Clinical, microbiological, and echocardiographic data. The following data were collected from the patients at admission and during hospitalization: age, sex, and Charlson comorbidity index (19); history of diabetes, cancer, intravenous drug use, underlying heart disease, chronic renal insufficiency, and heart failure; leukocyte count, serum CRP level, and causative pathogens (determined by blood culture, serology testing, valve culture, or polymerase chain reaction from a valve specimen according to international guidelines [20]); and indications for valve surgery. Transthoracic echocardiographic (TTE) and transesophageal echocardiographic (TEE) analyses were performed in all patients at admission, and the data were interpreted by experienced senior cardiologists as previously described (21). TTE and TEE were repeated weekly during the hospitalization period. Briefly, the echocardiographic data included the presence and maximal length of vegetations. Periannular complications were defined as an abscess, pseudoaneurysm, or fistula according to accepted definitions (2). The data were stored electronically and noted the time of the original examination without alteration. Valvular regurgitation was semiquantitatively assessed (22). The left ventricular ejection fraction was quantified using the Simpson biplane method.

Abbreviations and Acronyms

CI = confidence interval

CRP = C-reactive protein

CT = computed tomography

FDG = fluorodeoxyglucose

IQR = interquartile range

PET = positron emission tomography

PVE = prosthetic valve endocarditis

SUV_{max} = maximal standardized uptake value

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

^{18}F-fluorodeoxyglucose PET/CT. After eating a meal rich in fat and very low in carbohydrates to reduce the physiological uptake of FDG in the myocardium, the patients fasted for at least 12 h prior to PET/CT. Intravenous administration of 5 MBq/kg ^{18}F-FDG was performed after the blood glucose level (<1.8 g/l) was checked. PET and whole-body CT scans were carried out consecutively using a Discovery ST PET/CT scanner (General Electric, Milwaukee, Wisconsin) 1 h after ^{18}F-FDG injection. The PET data were acquired in 3-dimensional mode, and the images were corrected for attenuation and reconstructed using the OSEM (ordered-subset-expectation-maximization) algorithm. The PET data were linked with the CT data. The data analysis (Xeleris, General Electric) was based on visual interpretation and quantitative measurement of FDG uptake using the following criteria:

Visual analysis: hypermetabolic intensities in the prosthetic and periprosthetic areas were considered to be abnormal. This uptake had to be confirmed in the uncorrected images. This visual analysis defined whether the PET/CT was positive or negative.

Semiquantitative analysis: the intensity of FDG uptake was determined by measuring the maximal standardized uptake value (SUV_{max}), which was obtained by normalizing the tissue concentration of FDG activity and the patient's weight. SUV_{max} was calculated using an average of 3 measurements from 3 volumes of interest (5 mm^3) introduced in the prosthetic region at equal distances from each other. To obtain a background value for FDG uptake, blood SUV was determined by introducing 35-mm^3 volumes of interest within the right atrium in locations devoid of significant spillover activity. The prosthetic valve-to-background ratio was calculated by dividing the prosthetic valve SUV_{max} by the atrial blood SUV_{max}. This ratio allowed possible biases related to differences in the FDG metabolism to be overcome.

In addition, whole-body acquisition was performed to detect silent embolic events and septic metastases defined as extracardiac abnormal uptakes. Some abnormal uptakes could also correspond to the incidental discovery of tumors. The calculated mean radiation dose for a whole-body ^{18}F-FDG PET/CT was 15 mSv.

The images were interpreted by 2 nuclear medicine physicians who were blinded to the clinical data and the applied

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imaging convention. In the cases of disagreement, a consensus was reached via a third physician. Patient management was performed independently of the PET/CT results.

Gold standard. The final diagnosis was defined by an expert team according to the clinical and/or pathological modified Duke criteria determined from the data collected during a 3-month follow-up after admission (4). Follow-up after hospital discharge was actively conducted based on consultations at 1 and 3 months, TTE and/or TEE, blood cultures, and biological samples in our department or by contacting the patients or their physicians.

Statistical analysis. Continuous variables were expressed as the median (interquartile range [IQR]) and compared using the Mann-Whitney *U* test. Categorical data were expressed as numbers (percentages) and compared using the chi-square or Fisher exact test.

In the first analysis, we determined the diagnostic value of PET/CT (presence or absence of abnormal FDG uptake at the prosthetic valve site). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, as well as the 95% confidence interval (CI), were calculated using the final diagnoses of *definite* PVE and *rejected* PVE as the outcomes. The prosthetic SUV_{max} and SUV_{max}/right atrium ratio were compared among the *definite*, *possible*, and *rejected* final diagnoses using the Kruskal-Wallis test and post hoc Dunn test.

In the second analysis, we added abnormal FDG uptake at the prosthetic valve as an additional major criterion in the modified Duke classification. Then we compared the early diagnostic value at admission of this novel Duke classification (Duke-PET/CT) with the classic Duke classification (Duke) (Table 1). The sensitivities and specificities were compared using the McNemar test. The net reclassification index was calculated to assess the improvement in the diagnosis categorization (23).

The analysis was performed according to the Standards for Reporting of Diagnostic Accuracy guidelines (24). Three patients of the present population were previously described in a recent case report publication (15).

The interobserver variability of PET-CT was assessed using the kappa test.

The analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois). All of the tests were 2 sided. A p value <0.05 was considered to be significant.

Results

Baseline characteristics. Seventy-two patients with suspected PVE were included during the study period (Fig. 1). The median age of the patients was 67 years (IQR: 60 to 76 years), and 61% were male. The baseline characteristics are summarized in Table 2. At the end of follow-up, the final diagnosis was classified as *definite* PVE in 30 patients, *rejected* PVE in 20, and *possible* PVE in 22. Fifty-nine patients received antibiotic treatment during hospitalization. Of the 29 patients who underwent cardiac surgery,

Table 1 Definition of Prosthetic Valve Endocarditis According to the Proposed Modified PET/CT Duke Criteria

***Definite* infective endocarditis**
Pathological criteria
1. Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen or
2. Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
Clinical criteria
1. 2 major criteria or
2. 1 major criterion and 3 minor criteria or
3. 5 minor criteria
***Possible* infective endocarditis**
1. 1 major criterion and 1 minor criterion or
2. 3 minor criteria
***Rejected* infective endocarditis**
1. Firm alternate diagnosis explaining evidence of infective endocarditis or
2. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days or
3. No pathological evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days or
4. Does not meet criteria for possible infective endocarditis, as above
Major criteria
Blood culture positive for infective endocarditis
Typical microorganisms consistent with infective endocarditis from 2 separate blood cultures
Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus* or
Community-acquired enterococci, in the absence of a primary focus or
Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows
≥2 positive cultures of blood samples drawn >12 h apart or
all of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
Evidence of endocardial involvement
Echocardiogram (TTE and/or TEE) positive for infective endocarditis defined as follows
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation or
Abscess or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Positive ^{18}F-FDG PET/CT: abnormal FDG uptake at the site of prosthetic valve
Minor criteria
Predisposition, predisposing heart condition, or injection drug use
Fever, temperature >38°C
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis

In the underlined text, the novel major criterion has been added to the previous modified Duke classification.

FDG = fluorodeoxyglucose; HACEK = *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IgG = immunoglobulin G; PET/CT = positron emission tomography/computed tomography; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

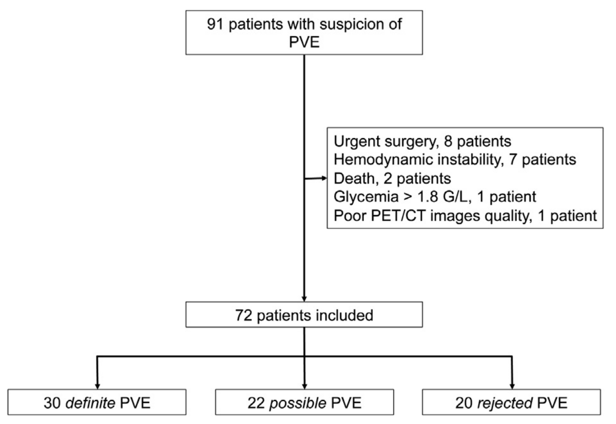

Figure 1 **Study Flow Chart**

Of the 91 patients with suspicion of prosthetic valve endocarditis (PVE), 72 were included and classified according to the final diagnosis determined using the modified Duke criteria established after a 3-month follow-up. PET/CT = positron emission tomography/computed tomography.

PVE was pathologically proven in 13 individuals. The indications for surgery were heart failure (n = 16), peri-annular abscess (n = 12), and high embolic risk (n = 8). Surgery consisted of implantation of bioprosthesis (n = 22), homograft (n = 5), and mechanical prosthesis (n = 2).

Diagnostic value of cardiac PET/CT. PET/CT was performed at a median time of 6 days (IQR: 4 to 11 days) after admission, 30 days (IQR: 6 to 46 days) after onset of symptoms, and 1,484 days (IQR: 526 to 3,396 days) after implantation of the prosthetic valve. In the 55 patients who received antibiotic therapy, PET/CT was performed at a median time of 9 days (IQR: 5 to 19 days) after the beginning of this treatment. A total of 36 of the patients (50%) showed abnormal FDG uptake at the prosthetic valve (positive PET/CT). There was no difference in the rate of positive PET/CT between patients with biological and mechanical prosthetic valves (52% vs. 46%; p = 0.63). The interobserver reproducibility was 86% (kappa = 0.71).

The results of PET/CT according to the final diagnosis are summarized in Table 3. The sensitivity, specificity, positive predictive value, negative predictive value, and global accuracy were 73% (95% CI: 54% to 87%), 80% (95% CI: 56% to 93%), 85% (95% CI: 64% to 95%), 67% (95% CI: 45% to 84%), and 76% (95% CI: 63% to 86%), respectively. Among the 13 patients with pathologically proven PVE, the PET/CT results were positive in 12 patients (92%), whereas echocardiography on admission was positive in only 7 patients (54%). Among the 7 patients who underwent surgery with a negative PET/CT, none had a pathologically proven PVE.

PET/CT was positive in 4 patients with a *rejected* PVE diagnosis (false positive 15%). Two of these individuals showed abnormal FDG uptake in an ascending aortic graft implanted with a prosthetic valve. In these 2 cases, it was difficult to determine whether the abnormal FDG uptake involved the prosthetic valve or only the aortic root. Additionally, 1 patient exhibited mechanical prosthesis thrombosis with negative tissue culture results after surgery and 1 presented an acute mitral chordae rupture associated with low FDG uptake in the aortic bioprosthetic valve, which appeared normal based on echocardiography. Eight patients with *definite* PVE showed normal cardiac PET/CT results (false negative 33%). PET/CT was conducted in these patients at a median time of 8.5 days (IQR: 4 to 13 days) after starting antibiotics; in the patients with *definite* PVE and positive PET/CT, this analysis was performed after a median time of 7 days (IQR: 5 to 16 days) (p = 0.85). The serum CRP level was higher in patients with positive PET/CT, but the difference was not statistically significant (56 mg/l [IQR: 10 to 116 mg/l] vs. 64 mg/l [IQR: 12 to 158 mg/l]; p = 0.43]). Figure 2 shows examples of PET/CT results.

Table 2 **Baseline Characteristics of the 76 Patients With PVE Suspicion**

Age, yrs	67 (60–76)
Male	44 (61)
Diabetes	17 (24)
History of cancer	9 (13)
Comorbidity index	4 (2–6)
Type of prosthesis	
Bioprosthetic valve	44 (61)
Mechanical valve	28 (39)
Biology	
CRP, mg/l	22 (7–98)
White cells, 10^9/l	8 (6–11)
Causative pathogen	
Positive blood cultures	24 (33)
Staphylococcus aureus	16 (22)
Enterococcus faecalis	7 (10)
Streptococcus bovis	4 (6)
Other streptococci	2 (3)
Coagulase-negative staphylococci	3 (4)
Others	10 (14)
Echocardiography	
Vegetation	27 (38)
Periannular complications	8 (11)
New partial dehiscence	13 (18)
LVEF <45%	7 (10)
Cardiac surgery	29 (40)

Values are median (interquartile range) or n (%).
CRP = C-reactive protein; LVEF = left ventricular ejection fraction; PVE = prosthetic value endocarditis; other abbreviation as in Table 1.

Table 3 **Results of PET/CT According to the Final Diagnosis**

	Final Diagnosis		
	Definite PVE	*Possible* PVE	*Rejected* PVE
Positive PET/CT	22 (73)	10 (45)	4 (20)
Negative PET/CT	8 (27)	12 (55)	16 (80)

Values are n (% of each final diagnosis).
Abbreviations as in Tables 1 and 2.

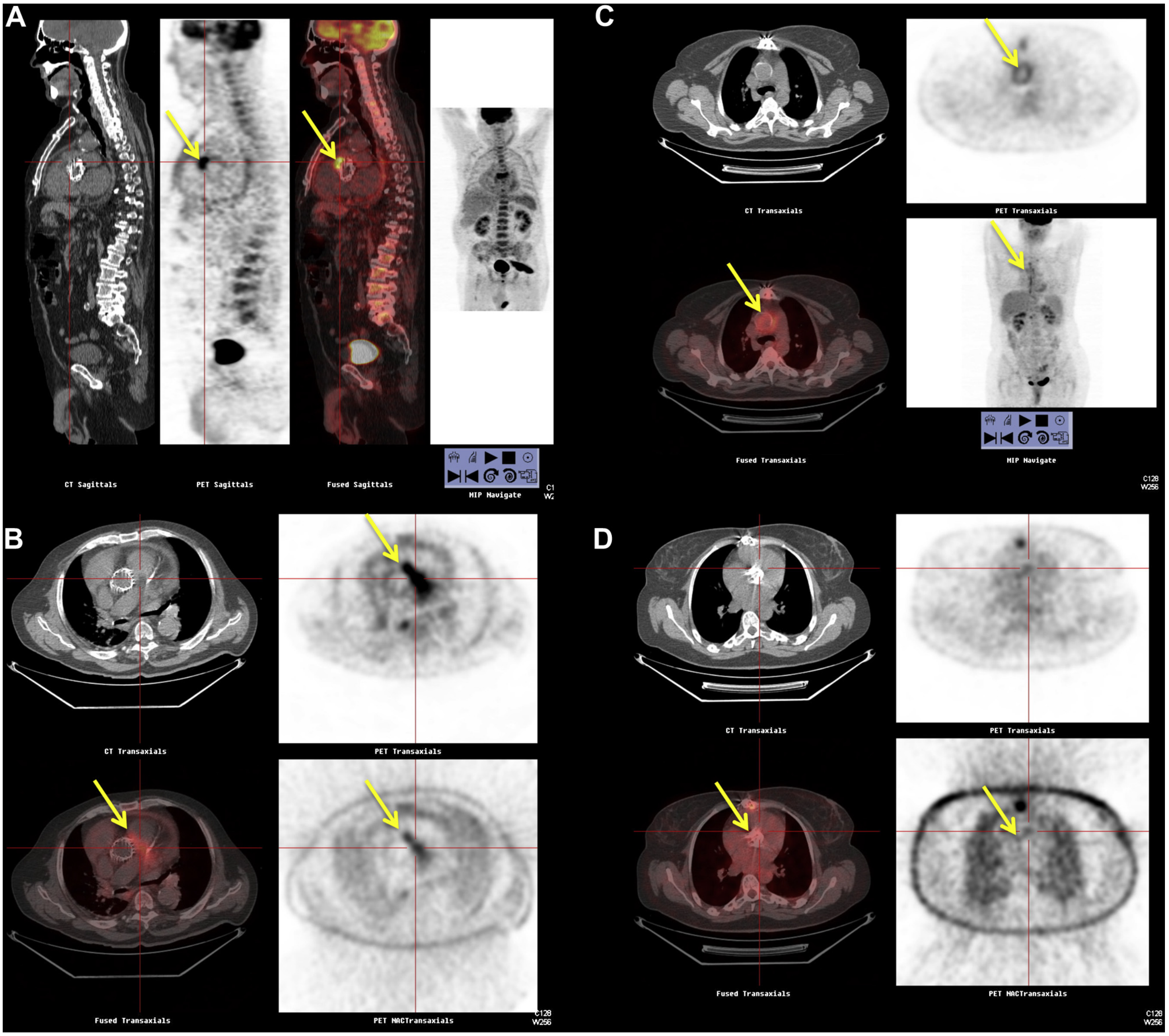

Figure 2 **Examples of True- and False-Positive PET/CT Results**

(A and B) PET/CT results in a patient with a *definite* diagnosis of PVE 22 days after a transcatheter aortic valve implantation (Corevalve). The high fluorodeoxyglucose (FDG) uptake **(yellow arrows)** is observed at the level of the anterior aortic annulus, where an abscess was confirmed by echocardiography and during surgery. The maximal standardized uptake value (SUV_{max}) was 7 g/ml. **(C and D)** PET/CT results in a patient with a *rejected* diagnosis of PVE but an abnormal uptake of FDG **(yellow arrows)** at the level of an aortic root graft and next to a mechanical aortic prosthetic valve (Bentall procedure). This false-positive result might be explained by an inflammatory response to the BioGlue surgical adhesive (a topically applied mixture of bovine serum albumin and glutaraldehyde) used to seal the aortic root graft. The SUV_{max} was 2.9 g/ml. Abbreviations as in Figure 1.

Among the 30 patients with *definite* PVE, 15 patients (50%) exhibited both a positive initial echocardiogram at admission and positive PET/CT, 7 patients (23%) presented a positive PET/CT despite a negative initial echocardiogram, and 8 patients (27%) exhibited a negative PET/CT despite a positive initial echocardiogram. Thus, no patient with *definite* PVE displayed both a negative initial echocardiogram and negative PET/CT. Of the 12 patients with a positive PET/CT and negative initial echocardiography, 7 had a *definite* PVE, and a periprosthetic abscess was identified in 6 individuals during repeated echocardiographic study (Fig. 3) performed at a median time of 8 days (IQR: 7 to 23 days).

The PET/CT was positive in 11 of the 20 patients (55%) with only a vegetation shown in the initial echocardiogram, 5 of the 8 patients (63%) presented periannular complications, and 7 of the 13 patients (54%) exhibited new partial dehiscence of the prosthetic valve (Table 4).

The semiquantitative analysis of FDG uptake showed a significant higher prosthetic valve SUV_{max} in patients with

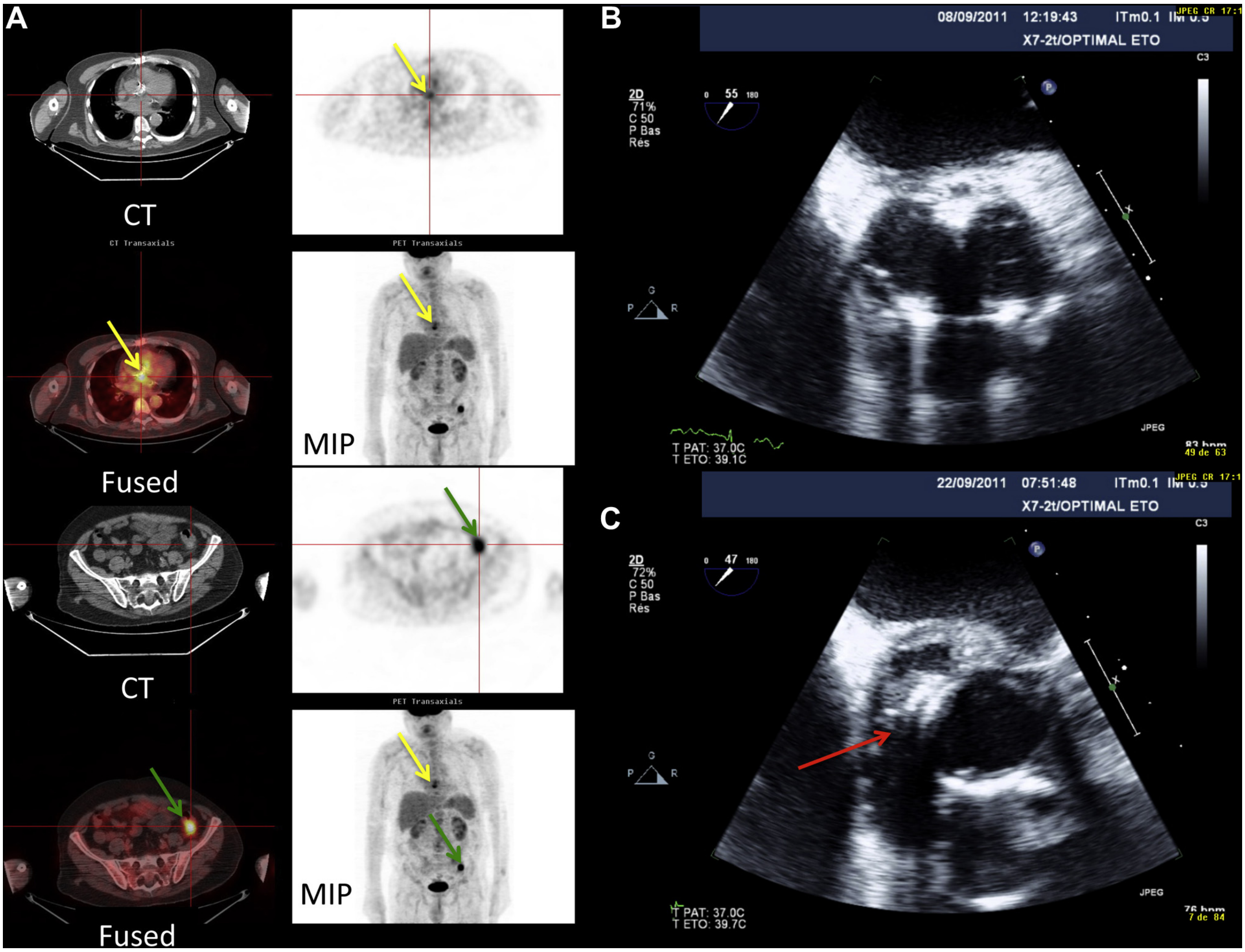

Figure 3 **Example of Positive PET/CT in a Patient With PVE and Normal Initial Echocardiography**

The first transesophageal echocardiogram did not show any abnormalities around the aortic bioprosthetic annulus **(B)**. The second transesophageal echocardiogram, performed at the end of antibiotic treatment (1 month later), showed a large periprosthetic abscess **(C, red arrow)**. The ^{18}F-FDG PET/CT performed 3 days after the first echocardiogram showed an abnormal uptake around the aortic prosthesis **(A, yellow arrow)** and another hyperintensity in the left colon, revealing a cancer **(A, green arrow)** that was confirmed by colonoscopy. The PET/CT images are presented as fused (PET+CT) and attenuation-corrected maximal intensity (MIP) projection images. Abbreviations as in Figures 1 and 2.

definite PVE in comparison with the other groups and trend toward a higher prosthetic valve-to-background SUV_{max} ratio (Fig. 4).

Cardiac PET/CT as a major Duke criterion. The addition of abnormal FDG uptake at the site of the prosthetic valve as a novel major criterion significantly increased the sensitivity of the modified Duke criteria established at admission (70% [95% CI: 52% to 83%] vs. 97% [95% CI: 83% to 99%]; $p = 0.008$). This result was the consequence of a significant reduction ($p < 0.0001$) in the number of *possible* PVE cases from 40 (56%) to 23 (32%). With this strategy, the specificity was not significantly decreased (50% [95% CI: 30% to 70%] vs. 40% [95% CI: 22% to 61%]; $p = 0.5$) (Table 5). The net reclassification index was 10.3%. The results of the Duke and Duke-PET/CT criteria are summarized for all of the patients in the Online Appendix, Online Table 1.

Table 4 **Results of PET/CT According to the Results of the Initial Echocardiography Study (TTE and TEE)**

	Positive PET/CT	Negative PET/CT	p Value
Vegetation	16 (59)	11 (41)	0.22
Periannular complications	5 (63)	3 (37)	0.71
New partial dehiscence	7 (54)	6 (46)	0.76

Values are n (% of each echocardiographic result).
Abbreviations as in Table 1.

Whole-body PET/CT to detect emboli, distant infection, and portal of entry. Whole-body PET/CT identified emboli and distant infection in 8 patients (3 splenic emboli and 5 spondylodiscitis). Only one of these lesions was silent. Thus, the results of applying this technique did not significantly improve the value of the modified Duke criteria. In

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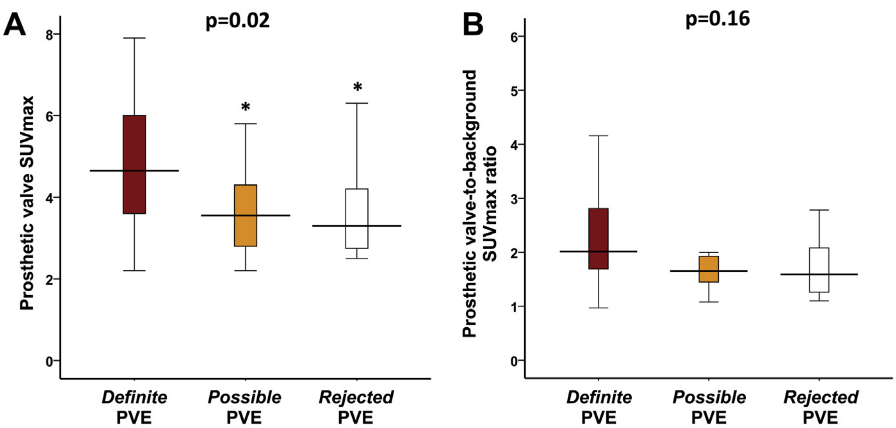

Figure 4 **Results of the Prosthetic Valve SUV_{max} and Prosthetic Valve-to-Background SUV_{max} Ratio According to the Final Diagnosis**

The SUV_{max} was significantly higher in patients with *definite* PVE in comparison with the 2 other groups **(A)**, whereas the prosthetic valve-to-background SUV_{max} ratio was not significantly higher **(B)**. $^*p < 0.05$. Abbreviations as in Figures 1 and 2.

addition, 8 patients had a colonic abnormal FDG uptake. Among them, colonoscopy with biopsies identified cancer in 2 patients and low-grade dysplasia in 3 patients.

Discussion

PVE represents a diagnostic challenge. The present study tested the use of ^{18}F-FDG PET/CT for diagnosing PVE. We demonstrated that this imaging technique has good diagnostic value, especially when abnormal FDG uptake around the prosthetic valve was added as a major criterion to the modified Duke classification established within a few days after admission. The inclusion of this new criterion significantly increased the sensitivity of the modified Duke classification and allowed for an earlier diagnosis, especially when echocardiography was normal or doubtful.

The early diagnosis of endocarditis is of crucial importance because a delay in antibiotic therapy and cardiac surgery has negative effects on clinical outcomes (3,25). However, diagnosis of this condition is often difficult, especially in the presence of foreign materials such as pacemaker/defibrillator leads and prosthetic valves. In such a situation, echocardiography shows a decreased sensitivity and specificity (2,26). Therefore, efforts have been made to develop new imaging strategies to accelerate the diagnostic process. Although the interest in cardiac CT for use in some situations has increased (27), similar to echocardiography, cardiac CT is still a morphological imaging modality that lacks functional data, which is a major limitation when microbiological data are negative and in the case of absent or doubtful structural lesions. Labeled leukocyte scintigraphy is another option for imaging, but this technique is time consuming (28). By measuring metabolic tissue activity, ^{18}F-FDG PET/CT has emerged as a promising method for diagnosing cardiovascular infections (29). In a large contemporary cohort of patients with presumed PVE, we found that the sensitivity and specificity of this technique were 73% and 80%, respectively. These results were similar to data from Bensimhon et al. (12) on pacemaker lead endocarditis. Although these results are good, we cannot conclude that PET/CT alone is the "magic" modality capable of diagnosing any PVE episodes. Indeed, such an imaging test is difficult to imagine for a complex disease such as endocarditis. However, when the results of PET/CT were taken into account together with other clinical, microbiological, and echocardiographic parameters, our findings showed that the sensitivity of the modified Duke criteria dramatically increased to 97%, a rate never reported previously for this disease. This result was obtained without compromising specificity. Moreover, the inclusion of cardiac PET/CT in the diagnostic strategy demonstrated the potential of the modified Duke criteria to provide a diagnosis earlier in the course of the disease because the criteria were initially developed to define cases of endocarditis for epidemiological studies conducted at the end of patient follow-up (4).

Table 5 **Diagnostic Value of the Modified Duke Criteria at Admission With (Duke-PET/CT) and Without the Implementation of the PET/CT Results**

	Final Diagnosis		
	Definite PVE	*Possible* PVE	*Rejected* PVE
Duke			
Definite PVE	21 (70)	0 (0)	0 (0)
Possible PVE	8 (27)	22 (100)	10 (50)
Rejected PVE	1 (3)	0 (0)	10 (50)
Duke-PET/CT			
Definite PVE	29 (97)	10 (45)	2 (10)
Possible PVE	1 (3)	12 (55)	10 (50)
Rejected PVE	0	0	8 (40)

Values are n (% of each final diagnosis).
Abbreviations as in Tables 1 and 2.

As previously suggested, the major contribution of PET/CT to the early diagnosis of PVE appears to be related to cases for which the initial echocardiographic analysis is negative (15). In addition, abnormal FDG uptake was observed before the appearance of infectious damage in echocardiography in several patients, which highlights the power of PET/CT to reveal infection before significant damage has occurred. Our medical team has recently proposed the inclusion of PET/CT in the strategy of the difficult diagnosis of Q fever endocarditis, for which echocardiography usually shows atypical lesions (30).

The improvement in the sensitivity of the modified Duke criteria obtained by including the PET/CT data resulted from a significant decrease in the rate of *possible* PVE diagnoses. The *possible* PVE group has represented a problem in therapeutic decision making because of the potential delay in initiating antibiotic treatment, which can lead to severe complications, such as embolism, cerebral hemorrhage, and acute heart failure. By reclassifying the majority of *possible* PVE cases to *definite* PVE, PET/CT might have an impact on therapeutic strategies and clinical outcomes in the future.

Study limitations. Although the results of the PET/CT analysis are encouraging, we did observe false-positive and false-negative tests. The few *definite* PVE cases with negative PET/CT might be explained by the patients presenting disease with a lower inflammatory activity or PET/CT that was performed too long after initiating antibiotic therapy. The optimal timing for performing PET/CT, according to the onset of antibiotic treatment, should be determined in future studies. In addition, false-positive results of PET/CT may occur when this technique is performed too early after the implantation of the prosthetic valve (31). In the present study, the patients with cardiac surgery performed <1 month earlier were not included to avoid these false-positive results related to the early post-operative inflammation around the sewing ring. We identified other possible causes of false positives, such as severe prosthetic thrombosis or the presence of an aortic root graft. In the latter case, abnormal FDG could be related to the BioGlue surgical adhesive (a topically applied mixture of bovine serum albumin and glutaraldehyde) used to seal the aortic root graft, as reported by Schouten et al. (32). The limited spatial resolution of the PET/CT used in this study did not allow us to determine whether the FDG uptake was present only on the aortic root graft or also involved the prosthetic valve.

The final diagnosis determined according to the results of modified Duke criteria at the end of the follow-up was used as the gold standard in this study. Although this choice could be criticized, this decision allowed the inclusion of patients in whom surgical specimens could not be systematically obtained because of a nonsurgical therapeutic strategy. Furthermore,

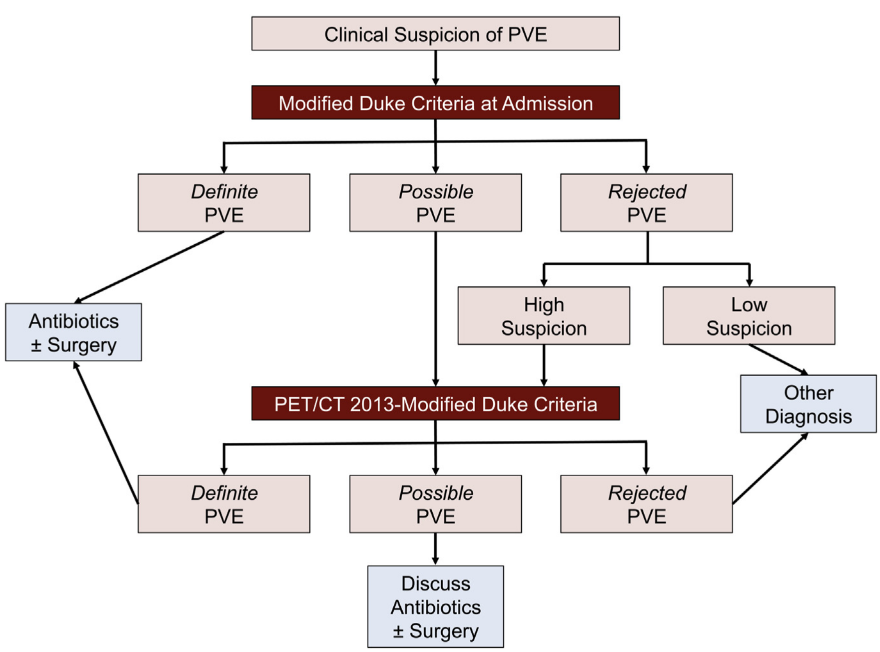

Figure 5 **Proposed Algorithm for Evaluating Patients With Suspected PVE Using PET/CT**

This algorithm integrates the results of the present study by implementation of PET/CT in the diagnostic strategy of patients in whom the diagnosis of PVE remains uncertain after the initial evaluation using the modified Duke criteria. Thus, in case of *possible* PVE, or *rejected* PVE associated with high clinical suspicion, a new evaluation should be performed by using the PET/CT 2013-modified Duke criteria. These new criteria will allow the detection of more *definite* diagnoses thanks to a higher sensitivity. Abbreviations as in Figure 1.

the favorable results regarding PET/CT sensitivity were confirmed when a surgical specimen positive for infection was used as the gold standard.

Conclusions

The ^{18}F-FDG PET/CT imaging technique was useful for diagnosing PVE. This imaging modality is not a substitute for clinical, microbiological, and echocardiographic evaluation but could be implemented in the global assessment of patients with suspected PVE. By demonstrating the potential role of this methodology in early diagnosis, especially in the case of initial negative echocardiography results, we showed the significant diagnostic impact when positive PET/CT was used as a novel major Duke criterion. Moreover, whole-body imaging was also useful for detecting emboli, metastatic infection, and occult primary tumors. Based on these results, we have proposed an algorithm for incorporating PET/CT in the evaluation of patients with suspected PVE (Fig. 5). Future large-scale studies will be necessary to confirm whether this strategy is cost effective.

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Key Words: cardiac imaging ■ diagnosis ■ endocarditis ■ positron emission tomography ■ prosthetic valve.

APPENDIX

For a supplemental table, please see the online version of this article.