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NEW RESEARCH PAPER

Diagnostic Value of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography Computed Tomography in Prosthetic Pulmonary Valve Infective Endocarditis

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ABSTRACT

OBJECTIVES The aim of this study was to assess the diagnostic performances of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) in congenital heart disease (CHD) patients with pulmonary prosthetic valve or conduit endocarditis (PPVE) suspicion.

BACKGROUND PPVE is a major issue in the growing CHD population. Diagnosis is challenging, and usual imaging tools are not always efficient or validated in this specific population. Particularly, the diagnostic yield of ^{18}F-FDG PET/CT remains poorly studied in PPVE.

METHODS A retrospective multicenter study was conducted in 8 French tertiary centers. Children and adult CHD patients who underwent ^{18}F-FDG PET/CT in the setting of PPVE suspicion between January 2010 and May 2020 were included. The cases were initially classified as definite, possible, or rejected PPVE regarding the modified Duke criteria and finally by the Endocarditis Team consensus. The result of ^{18}F-FDG PET/CT had been compared with final diagnosis consensus used as gold-standard in our study.

RESULTS A total of 66 cases of PPVE suspicion involving 59 patients (median age 23 years, 73% men) were included. Sensitivity, specificity, positive predictive value, and negative predictive value of ^{18}F-FDG PET/CT in PPVE suspicion were respectively: 79.1% (95% CI: 68.4%-91.4%), 72.7% (95% CI: 60.4%-85.0%), 91.9% (95% CI: 79.6%-100.0%), and 47.1% (95% CI: 34.8%-59.4%). ^{18}F-FDG PET/CT findings would help to correctly reclassify 57% (4 of 7) of possible PPVE to definite PPVE.

CONCLUSIONS Using ^{18}F-FDG PET/CT improves the diagnostic accuracy of the Duke criteria in CHD patients with suspected PPVE. Its high positive predictive value could be helpful in routine to shorten diagnosis and treatment delays and improve clinical outcomes. (J Am Coll Cardiol Img 2021;■:■-■) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

^{18}F-FDG = ^{18}F-fluorodeoxyglucose

CHD = congenital heart disease

DC = Duke criteria

IE = infective endocarditis

PET/CT = positron emission tomography/computed tomography

PPVE = pulmonary prosthetic valve or conduit endocarditis

RVOT = right ventricular outflow tract

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Infective endocarditis (IE) is a complex and life-threatening disease leading to an in-hospital and 6 months mortality of 20% and 30%, respectively (1). About 30% of IE cases involve prosthetic valves or electronic devices, and the vast majority concerns left-sided prostheses in elderly patients (1-3). Among less-common right-sided IE, patients with congenital heart diseases (CHD) are particularly represented but are still less studied. Overall IE incidence in CHD patients is 1.33 per 1,000 person-years (4), and 50% to 60% of the cases involve the right heart, with a high proportion of pulmonary prosthetic valve or conduit endocarditis (PPVE) (5,6). Endocarditis affects both surgical substrates as pulmonary homografts or xenograft valved conduits (0.3 to 1.5 cases per 100 person-years [7,8]) and percutaneous valves (2.4 to 5.7 cases per 100 person-years [9-12]). The clinical signs of PPVE lack specificity, and atypical presentations with diagnostic wandering are common. Regarding the better-known left-sided prosthetic valve endocarditis, the integration of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) into the latest diagnostic criteria of European guidelines increased the diagnostic sensitivity by 52%-70% to 91%-97% (3,13). To our knowledge, only 1 monocentric study focused on ^{18}F-FDG PET/CT diagnostic yield in CHD patients suspected of IE. However, the latter results were limited by the small size of the studied population, including only 25 patients with 11 pulmonary valve prostheses (14). On the basis of the limited available data in this field, we aimed to evaluate the diagnostic performance of ^{18}F-FDG PET/CT in the diagnosis of PPVE in CHD patients.

METHODS

STUDY DESIGN. In this nationwide multicenter study, patients from 8 French CHD tertiary referral centers who underwent ^{18}F-FDG PET/CT for suspicion of PPVE were retrospectively included. The primary endpoint was the diagnostic performance of ^{18}F-FDG PET/CT (sensitivity, specificity, and positive and negative predictive values) in CHD patients with PPVE suspicion. The participating centers were the University Hospitals of Bordeaux, Marseille, Toulouse, Grenoble, Nantes, Amiens, and Paris (European Hospital Georges Pompidou and Marie Lannelongue Hospital). Data of all consecutive children and adult CHD patients with right ventricular outflow tract (RVOT) prosthetic material who underwent ^{18}F-FDG PET/CT for PPVE suspicion between January 2010 and May 2020 were reviewed. The involved RVOT prosthetic substrates included the following: percutaneous pulmonary valved stents (Melody, Medtronic Inc; and Sapien, Edwards Lifesciences devices), surgical pulmonary bioprostheses, right ventricle to pulmonary artery prosthetic conduits, and pulmonary homografts. A minimal available follow-up of 3 months was required for all patients. There was no restriction on the time interval between surgery or percutaneous procedure and PET/CT. The study was approved by the Institutional Review Board of University Hospital of Bordeaux, France.

DATA COLLECTION. Patient data. Patients' data were anonymously collected. The type of CHD defect and patients' surgical history were recorded, including type and size of all cardiac prosthetic material. Comorbidities, usual treatment, and the Charlson score at baseline were collected. Symptoms and clinical features occurring before and during suspected IE episode were also noticed. Fever was defined as a temperature >38 °C (15). The following echocardiographic findings were recorded: presence of pulmonary valve/conduit vegetation, paravalvular complications, and RVOT hemodynamic features (transvalvular peak velocity and valvular regurgitation). Vegetations and paravalvular complications were recorded as a positive transthoracic echocardiography (TTE) or transesophageal echocardiography

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(TEE) and as major criterion for IE diagnosis (15). Data from classical work-up CT scan, cardiac CT scan, or labeled white blood cells scintigraphy were also collected when available. Blood cultures were scored as positive if at least 1 was positive before or during clinical admission. The final microbiological diagnosis was recorded taking into account repeated blood cultures, serology results, explanted prosthesis cultures, and 16S ribosomal RNA polymerase chain reaction. C-reactive protein (CRP), leukocyte, and neutrophil levels on the day of the PET/CT date were recorded. Based on clinical, microbiological, and imaging data, the current Duke classification was obtained and allowed to consider IE as definite, possible, or rejected (15).

PET/CT data. We recorded the date of PET/CT examinations and details of patient preparation and acquisition procedure. The parameters of ^{18}F-FDG uptake foci were recorded: ^{18}F-FDG abnormal uptake in the pulmonary prosthesis area (homogeneous or heterogeneous uptake), presence of other uptake foci, the maximal Standardized Uptake Value (SUV max) in the targeted area, and the presence of extracardiac foci (related to embolization, sepsis entry point, or another lesion). The final conclusion of nuclear physicians was recorded as positive, negative, or unclear examination. Real-life reviews of PET/CT examinations were used to calculate test performance.

Follow-up. Follow-up duration was the time between PET/CT and the last patient's work-up. The clinical outcomes, the function of infected RVOT prothesis, and the occurrence of IE recurrence were recorded at the end of follow-up.

GOLD STANDARD AND PATIENT CLASSIFICATION. The final diagnosis was retained by a single dedicated "endocarditis team" and used as the "gold standard." All patient records have been reviewed by this expert committee, composed of infectious disease specialists, cardiologists, and pediatric cardiologists from the principal investigator center and for the specific purpose of this study. IE was considered as definite, possible, or rejected according to the endocarditis team consensus, based on modified Duke criteria (DC) and all medical record elements except the PET/CT. Indeed, physicians of endocarditis team were blinded to the PET/CT result (even though the interpretation of the PET/CT was done unblinded by the nuclear physicians at each center).

TABLE 1 Demographic and Clinical Data at Baseline (n = 66)

Patient characteristics	
Male	48 (72.7)
Age, y	23.4 (18.2-33.4)
Weight, kg	60 (50-70)
Height, cm	170 (162-175)
Comorbidities	
Diabetes	1 (1.5)
Pulmonary hypertension	5 (7.6)
Chronic respiratory failure or severe lung disease	3 (4,5)
Chronic renal failure	2 (3.0)
Hepatic failure	2 (3.0)
Autoimmune disease	2 (3.0)
Mental retardation	9 (13.6)
Disabling neurological disease	6 (9.1)
Immunodepression	7 (10.6)
Genetic syndrome	14 (21.2)
22q11.2 deletion syndrome	6 (9.1)
Down syndrome	1 (1.5)
Other polymalformative illness	7 (10.6)
Charlson score	
0	51 (77.3)
1	9 (13.6)
≥2	6 (9.1)
Treatment	1 (1.5)
Antiplatelet	34 (51.5)
Anticoagulant	8 (12.1)
Type of CHD	
Tetralogy of Fallot	15 (22.7)
Ross/aortic disease	14 (21.2)
Pulmonary atresia with VSD	11 (16.7)
Double outlet right ventricle	7 (10.6)
Complex transposition of great arteries	6 (9.1)
Congenital pulmonary stenosis	3 (4.5)
Truncus arteriosus	3 (4.5)
PA with intact ventricular septum	1 (1.5)
Other complex CHD	6 (9.1)
Type of RV-PA substrate	
Pulmonary surgical bioprosthesis	9 (13.6)
Pulmonary homograft	13 (19.7)
Freestyle valve[a]	6 (9.1)
Contegra conduit	15 (22.7)
Hancock conduit	13 (19.7)
Dacron/Gore-Tex conduit or patch	9 (13.6)
Unspecified RV-PA conduit	7 (10.6)
Melody valved stent	32 (48.5)
Sapien valved stent	1 (1.5)
Presence of electronic device	13 (19.7)
Endocardial pacemaker	6 (9.1)
Endocardial defibrillator	6 (9.1)
Epicardial pacemaker	1 (1.5)

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STATISTICAL ANALYSIS. Continuous variables were presented as the median and 25th to 75th percentile (interquartile range). Categorial data were expressed as counts and percentages. Patients with definite and rejected IE final diagnosis were considered for the analysis of PET/CT test performance. We determined the diagnostic performance of PET/CT (sensitivity, specificity, positive predictive value, negative predictive value, and their 95% CIs) compared with the gold standard. Accuracy of PET/CT was assessed by

TABLE 1 Continued

Clinical presentation at admission	
Fever	53 (80.3)
Heart failure signs	7 (10.6)
Immunological or vascular IE signs	33 (50)
Septic pulmonary infarcts	26 (39.4)
Major systemic arterial emboli	2 (3.0)
Glomerulonephritis	4 (6.1)
Osler's nodes	1 (1.5)
Septic shock	5 (7.6)

Values are n (%) or median (interquartile range). [a]Freestyle valve (Medtronic) is a stentless surgical full-root bioprosthesis, listed separately from other surgical bioprostheses.

CHD = congenital heart disease; IE = infective endocarditis; PA = pulmonary atresia; RV-PA = right ventricle to pulmonary artery; VSD = ventricular septal defect

the percentage of well-evaluated cases. On the basis of the Bayes theorem and according to our results, a 66.7% prevalence of IE was used for the calculations. The analysis was performed according to the Standards for Reporting of Diagnostic Accuracy guidelines (16), using R software version 4.0.1.(R Foundation for Statistical Computing).

RESULTS

CLINICAL DATA. A total of 66 PPVE suspicion episodes involving 59 patients (median age 23.4 years [18.2 years-33.4 years], 72.7% men) were included from January 2010 to May 2020. The clinical characteristics of the patients at baseline are summarized in Table 1. Ten patients were <15 years of age at diagnosis. The median age of these pediatric patients was 12.5 years and the youngest was 5 years. Fever was reported in 86% of patients in the definite IE group, 80% in the possible IE group and 58% in the rejected IE group.

TABLE 2 Microbiological and Inflammatory Features

	Total (N = 66)	Definite (n = 44)	Possible (n = 10)	Rejected (n = 12)
Microbiological features				
Positive blood culture[a]	49 (74.2)	39 (88.6)	9 (90.0)	1 (8.3)
Final germ identification	51 (77.3)	42 (93.2)	9 (90.0)	0
Staphylococcus aureus	11 (16.7)	10 (22.7)	1 (10.0)	0
CN staphylococcus	10 (15.2)	9 (20.5)	1 (10.0)	0
Streptococci spp	14 (21.2)	9 (20.5)	5 (50.0)	0
Viridans streptococci	11 (16.7)	6 (13.6)	5 (50.0)	0
HACEK group	4 (7.8)	4 (9.1)	0 (0.0)	0
Candida spp	3 (5.9)	3 (6.8)	0 (0.0)	0
Propionibacterium acnes	2 (3.9)	2 (4.5)	0 (0.0)	0
Other	7 (10.6)	5 (11.4)	2 (20.0)	0
Positive prothesis culture (n = 15)	4 (26.7)			
Positive 16S rRNA PCR (n = 3)	1 (33.3)			
Inflammatory findings[b]				
CRP, mg/L	45 (16.0-116.0)	67 (23.5-53.5)	35 (16.5-53.5)	5 (3.0-30.0)
Leukocytes, G/L	8.0 (6.3-11.0)	8.3 (6.6-11.2)	7.5 (5.5-10.7)	6.4 (6.1-8.9)
Neutrophils, G/L	5.9 (3.7-9)	6.4 (4.6-9.2)	4.7 (3.8-8.3)	4.1 (3.2-6.5)

Values are n (%) or median (interquartile range). [a]Blood cultures were considered as positive during the initial hospitalization, independently of microbiological criterion completion in Duke classification. [b]Inflammatory findings were recorded at the positron emission tomography/computed tomography date.

16S rRNA PCR = 16S ribosomal RNA polymerase chain reaction (performed on explanted prosthesis); CRP = C-reactive protein.

MICROBIOLOGICAL DATA. Microbiological findings are summarized in Table 2. Blood cultures at admission were positive for 74.2% (49 of 66) of the cases. Among the 44 definite IE, microbiological findings remained negative for only 2 cases. In those with definite IE diagnosis and negative blood cultures at admission, 2 patients had positive serologies (*Coxiella burnetii* and *Bartonella henselae)* and 1 had delayed positive blood culture because of HACEK group germ involvement. The most frequent pathogens were staphylococcus and streptococcus, both accounting for 68% of overall microbiological findings. In addition, many other rare germs were found: HACEK group's germs (n = 4); *Candida spp* (n = 3); *Propionibacterium acnes* (n = 2); and *Coxiella burnetii*, *Bartonella henselae*, *Abiotrophia defectiva*, *Kocuria varians*, *Lactobacillus,* and *Moraxella catarrhalis* (n = 1 each).

ANATOMIC AND HEMODYNAMIC FINDINGS. TTE/TEE and cardiac CT findings are displayed in Table 3. All patients underwent TTE, 22 (33.3%) underwent TEE and 44 (66.7%) underwent thoracic CT scan. At least 1 anatomical imaging examination (TTE, TEE, or cardiac CT) was positive in 27 cases (40.9%); all of them belonged to the definite IE group.

Among definite PPVE cases at final, median pulmonary transvalvular peak velocity in TTE was 3.6 m/s (3.0-4.5 m/s), whereas it was 3.2 m/s (2.2-3.7 m/s) in rejected cases. Transvalvular peak velocity increase—compared with the last known peak velocity value before IE suspicion—was 1.0 m/s (0.6-1.5 m/s) in the definite PPVE group vs 0.0 m/s (0.0-0.7 m/s) in the rejected PPVE group. A total of 11 patients (16.7%) presented a significant pulmonary regurgitation (moderate to severe).

PET/CT FINDINGS. The median interval between IE suspicion date and PET/CT was 7.5 days (5-13 days). Appropriate antibiotics were started before PET/CT for 55 patients (83.3%). Among them, the median delay between antibiotics onset and PET/CT was 7 days (4.0-9.8 days). Sufficient myocardial suppression was obtained in 92.5% of the cases. A total of 6 PET/CTs were performed within the 3 months after surgery: 2 within the first month and 4 between the first and the third month. The very early scans were both positive (1 true positive and 1 false positive). Of

the 4 scans performed between the first and the third month, 2 were true positives (postoperative delay of 42 and 62 days), 1 was false negative (postoperative delay of 77 days), and the last was "unclear" with final diagnosis of rejected PPVE (postoperative delay of 36 days). Of the 66 PET/CTs performed, 40 presented heterogenous or focal ^{18}FDG uptake, 10 homogenous ^{18}FDG uptake, and 16 no pathological ^{18}FDG uptake (Table 3). Among those with heterogenous or focal uptake, 39 (97.5%) were interpreted as positive for IE diagnosis. Among those with homogenous or no pathological uptake, none were considered by nuclear physicians as positive.

DIAGNOSTIC PERFORMANCE OF CARDIAC PET/CT. Classification of cases using DC, DC + PET/CT, and gold standard is shown in Table 4, and their diagnostic modification according to the PET/CT result is shown in Figures 1 and 2. The sensitivity, specificity, positive, and negative predictive values of ^{18}F-FDG PET/CT for diagnosis of PPVE were as follows: 79.1% (95% CI: 68.4%-91.4%), 72.7% (95% CI: 60.4%-85.0%), 91.9% (95% CI: 79.6%-100.0%), and 47.1% (95% CI: 34.8%-59.4%), respectively (Table 5). Based on gold standard, DC + PET/CT findings, 57% (4 of 7) of patients who were initially wrongly classified as possible IE would have been reclassified to definite IE. Among the 37 patients with positive PET/CT, 3 patients were finally considered as rejected IE (false positive rate: 8.1%). In these 3 cases, 2 had alternative diagnoses according to final endocarditis team judgment (1 isolated pacemaker infection and 1 cutaneous abscess) and the third had underwent PET/CT <1 month after Melody implantation. Among the 17 patients with negative PET/CT, 9 cases were finally considered as definite IE (false negative rate: 52.9%). The median time between antibiotics starting and PET/CT in these false negative cases was 2.5 days (1.8-4.8 days) and median CRP level was 56 mg/L (19-147 mg/L), whereas in true positive cases, this delay was 7.0 days (5.5-10.0 days) and median CRP level was 67.0 mg/L (25.5-135.5 mg/L). Indeed, inflammatory parameters appear slightly lower in false negatives as well as SUV max values. Also, there are more atypical germ IEs in the false-negative group (Table 6). The type of prosthesis was not associated with more false positives or negatives in PET/CT; in particular, bovine jugular vein prostheses do not lead to more false positives in our study (Table 7). Examples of true and false-positive PET/CT examinations are shown in Figure 3.

Among the 44 cases of definite PPVE, 27 patients (61.4%) exhibited both positive anatomical imaging examination (TTE/TEE or cardiac CT) and PET/CT, and 13 patients (29.5%) presented a positive PET/CT despite a negative anatomical imaging examination. Four patients with definite PPVE displayed both negative TTE/TEE/CT and negative PET/CT. The involved micro-organisms for these 4 last cases were: *Streptococcus sanguinis*, *Aggregatibacter actinomycetemcomitans* (HACEK group), *Candida parapsilosis,* and *Coxiella burnetii*. In the 30 definite IEs caused by streptococcus or staphylococcus, 24 (80%) PET/CTs were positive. In case of less common micro-organisms, PET/CT was positive in 8 of 12 (66.7%) definite PPVEs. A total of 11 patients (16.7%) underwent both PET/CT and labelled white blood cells scintigraphy, and their results were similar (both negative or both positive) in 8 of 11.

PERIPHERAL FINDINGS. Thoracic CT and PET/CT have allowed for a diagnosis of pulmonary septic

TABLE 3 Imaging Findings According to Final IE Diagnoses (n = 66)

	Definite PPVE (n = 44)	Possible PPVE (n = 10)	Rejected PPVE (n = 12)
Anatomic lesions			
Vegetation			
TTE or TEE	25 (56.8)	0 (0.0)	0 (0.0)
CT	7 (15.9)	0 (0.0)	0 (0.0)
Perivalvular complication			
TTE or TEE	1 (2.3)	0 (0.0)	0 (0.0)
CT	3 (6.8)	0 (0.0)	0 (0.0)
PET/CT cardiac findings			
Positive examination (n = 39)	34 (87.2)	2 (5.1)	3 (7.7)
Heterogenous or focal ^{18}F-FDG uptake (n = 40)	35 (79.5)	2 (20.0)	3 (25.0)
Homogenous ^{18}F-FDG uptake (n = 10)	2 (4.5)	3 (30.0)	5 (41.7)
No pathological ^{18}F-FDG uptake (n = 16)	7 (15.9)	5 (50.0)	4 (33.3)
SUV max in pulmonary valve area	4.6 (4.0-4.7)	3.8 (3.5-4.8)	4.1 (3.5-5.6)
Peripheral findings			
Pulmonary septic embolism at CT	13 (29.5)	1 (10.0)	0 (0.0)
Pulmonary septic embolism at PET/CT	23 (53.5)	1 (10.0)	0 (0.0)
Alternative diagnosis at PET/CT	1 (2.3)	1 (10.0)	3 (25.0)

Values are n (%) or median (interquartile range).

^{18}F-FDG = ^{18}F-fluorodeoxyglucose; CT = computed tomography; DC = Duke criteria; IE = infective endocarditis; PET/CT = positron emission tomography/computed tomography; PPVE = pulmonary prosthetic valve or conduit endocarditis; SUV max = maximal standardized uptake value; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

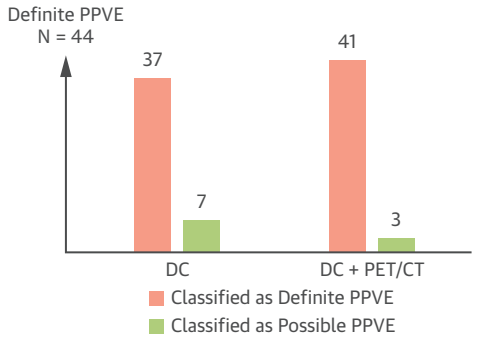
TABLE 4 PPVE Classification According to Diagnostic Approach (n = 66)

PPVE Classification	DC	PET/CT + DC	PET/CT	Gold Standard
Definite	37 (56.1)	43 (65.2)	39 (59.1)	44 (66.7)
Possible	18 (27.3)	15 (22.7)	3 (4.5)	10 (15.2)
Rejected	11 (16.7)	8 (12.1)	24 (36.4)	12 (18.2)

Values are n (%).

Abbreviations as in Table 3.

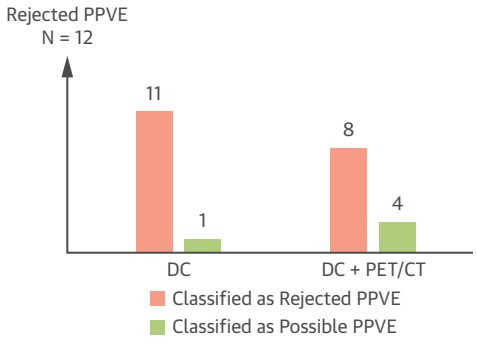
FIGURE 1 Classification of Definite PPVE According to DC With and Without PET/CT Result



Of the 44 cases of definite PPVE, 37 were correctly diagnosed as definite cases by the original Duke classification (without PET/CT). By including PET/CT in the Duke criteria, 4 more cases (n = 41) were correctly diagnosed as definite PPVE. DC = Duke criteria; PET/CT = positron emission tomography/computed tomography; PPVE = pulmonary prosthetic valve endocarditis.

embolism in 14 (28.6%) patients. All of them had definite (13 of 14) or possible (1 of 14) IE diagnosis at final. No mycotic aneurysm, intracranial ischemic, or hemorrhagic event was reported. PET/CT identified embolic and distant lesions in 31 patients: 24 cases of septic pulmonary embolization, 2 cases of extracardiac hypermetabolic lesion related to entry point (1 subcutaneous collection and 1 ENT-sphere infection), and 5 cases of differential diagnosis or incidentaloma. No neoplasia has been found by PET/CT in our population.

FIGURE 2 Classification of Rejected PPVE According to DC With and Without PET/CT Result



Of the 12 cases of rejected PPVE, 11 were correctly diagnosed as rejected cases by the original Duke classification (without PET/CT). By including PET/CT in the Duke criteria, 8 cases remain correctly diagnosed as rejected PPVE and 3 move to the "possible PPVE" category. Abbreviations as in Figure 2.

TABLE 5 Diagnostic Performances of PET/CT in PPVE Suspicions

Sensitivity	79.1 (68.4-91.4)
Specificity	72.7 (60.4-85.0)
Positive predictive value	91.9 (79.6-100)
Negative predictive value	47.1 (34.8-59.4)

Values are % (95% CI).
Abbreviations as in Table 3.

OUTCOMES. Median follow-up duration since the PET/CT was 26.6 months (10.0 months-44.7 months). At the end of follow-up and according to IE experts' consensus, the final diagnosis was classified as definite PPVE in 44 cases, was classified as possible in 10 cases, and was rejected in 12. Four cases were pathologically proven by cultures of explanted material. In the IE group, 33 of 44 patients (75%) required surgery during the follow-up, caused by post-endocarditis persistent lesions or uncontrolled infection. In total, 10 patients (15.2%) experienced a relapse or recurrence of IE during the follow-up. Only 1 patient (1.7%) died at the end of follow-up: a 50-year-old patient with tetralogy of Fallot and severe comorbidities who presented with an obstructive Melody valve infection. He died more than 7 months after PPVE diagnosis, following an undetermined septic episode.

DISCUSSION

To the best of our knowledge, this is the largest multicentric study evaluating the diagnostic yield of ^{18}F-FDG PET/CT in PPVE suspicion. In this cohort, we demonstrated a PET/CT sensitivity and specificity of 79.1% and 72.7%, respectively, as well as a high positive predictive value of 91.9%.

PET/CT DIAGNOSTIC YIELD AND PRACTICAL IMPLICATIONS. Our results are consistent with previously published data in left-sided valve and electronic device IE (13,17), although PET/CT specificity was lower in our series. Several elements may explain this finding: 1) because of the rarity of CHD, nuclear physicians are less familiar with RVOT features than left-sided valve prostheses; and 2) the difference between pathological and nonpathological ^{18}F-FDG uptake may be lower with some biological tissues, such as bovine jugular vein materials or pulmonary homografts, than substrates implanted in left-sided valves. Pulmonary homografts may cause a local immune response caused by the donor antigens persistence (18). This immunologic rejection evolves essentially in a chronic mode and may explain elevated ^{18}F-FDG uptake, even long-term after homograft implantation.

According to our findings, the main advantage of PET/CT in PPVE relates to its high positive predictive value (91.9%), providing an important benefit in clinical practice. As was already described in the overall prosthetic valve IE population (13), we found a significant improvement in the IE diagnostic accuracy when the PET/CT was integrated into DC. The ability of PET/CT to correctly reclassify doubtful cases is particularly relevant regarding the importance of early IE diagnosis to provide appropriate treatment and improve outcomes (19,20). This is all the more important given the relative weakness of classical imaging tools' sensitivity in the setting of PPVE (21). Indeed, we found that the presence of vegetation was not so frequently found in definite PPVE (25 of 44 in our study), making DC less sensitive in these patients. As well, the PET/CT added value, and its high sensitivity is even more useful to meet the imaging major criterion. The same conclusions are made by authors of a recent Belgian multicenter cohort study on Melody valve implanted patients (12): the number of definite IE diagnoses was lower than expected (15 of 23 cases) because of the low sensitivity of TTE/TEE and the limited use of other imaging tools (only 7 PET/CTs were performed, including 5 true positive examinations). Moreover, a significant increase in RVOT transvalvular gradient is a well-known sign in PPVE (10,12,21) and could be considered a reliable major criterion for some authors (22). Our results support this position given the clear difference in RVOT peak velocity between the definite PPVE group and the rejected PPVE group, and the recent nature of this gradient increase. However, our study was not designed to answer this interesting question.

Our results also highlight that the SUV max values are not directly related to the pathological nature of the FDG uptake on PET/CT. The qualitative interpretation of the uptake pattern (heterogeneous/focal vs homogeneous/circumferential uptake) is more relevant than maximal uptake intensity (23,24).

Some authors have emphasized the critical role of PET/CT as an integral part of the IE work-up to identify peripheral findings and help to rule in differential diagnosis (25-27). Accordingly, we also found that PET/CT was of value in detecting embolic complications (23 pulmonary embolisms detected by PET/CT). Among them, 43.5% were clinically silent and had not been seen in classical CT, possibly caused by a lower CT sensitivity. Another potential advantage of PET/CT in the CHD population is to assess the infection status of other devices, if any, to target only infected material to be removed. Thus, PET/CT is an integral part of the imaging work-up for suspected PPVE and provides metabolic information that complements the anatomical data (**Central Illustration**).

TABLE 6 Comparison of True Positives and False Negatives on Factors That May Affect PET/CT Sensitivity

	True Positives (n = 34)	False Negatives (n = 9)
Age, y	22.4 (17.5-30.5)	19.6 (13.6-23.1)
Male	26 (76.5)	6 (66.7)
Time from surgery to PET/CT, d	1,634 (381-2,347)	1,102 (910-3,061)
Homograft	4 (11.8)	1 (11.1)
BJV conduit/prosthesis	20 (58.8)	6 (66.7)
Immunodeficiency	2 (5.9)	1 (11.1)
Time from symptoms to PET/CT, d	16 (11-31)	23 (17-26)
Fever	30 (88.2)	7 (77.8)
Vegetation[a]	18 (52.9)	4 (44.4)
CRP,[b] mg/L	67 (26-136)	56 (19-147)
Leukocytes,[b] G/L	9.1 (6.6-11.2)	7.7 (5.9-8.6)
IE common germ[c]	24 (75.0)	4 (44.4)
Negative blood culture	3 (8.8)	2 (22.2)
Antibiotics before PET/CT	31 (91.2)	8 (88.9)
Time from antibiotics to PET/CT, d	7 (5.5-10.0)	2.5 (1.8-4.8)
SUV max on pulmonary prosthesis	4.9 (4.1-6.3)	2.6 (2.6-3.7)

Values are median (interquartile range) or n (%). [a]Visualized in TTE/TEE. [b]Values of biological parameters on the date of the PET/CT. [c]Common germs include all types of streptococci and staphylococci.

BJV = bovine jugular vein; CRP = C-reactive protein; IE = infective endocarditis; SUV = standardized uptake value; other abbreviations as in Table 3.

PET/CT DRAWBACKS. The PET/CT is a useful imaging tool, but it presents some limits to consider: the poor negative predictive value, radiation dose, constraints related to preparatory fasting, and temporality conditions to be respected to avoid false negatives and false positives. The low negative predictive value suggests that a negative PET/CT should not be weighed in the diagnostic process. Even though the preparatory diet may seem difficult for children, the youngest patient in our study was 6 years of age at PET/CT date and myocardial suppression was correctly obtained. Several authors showed that low systemic inflammation

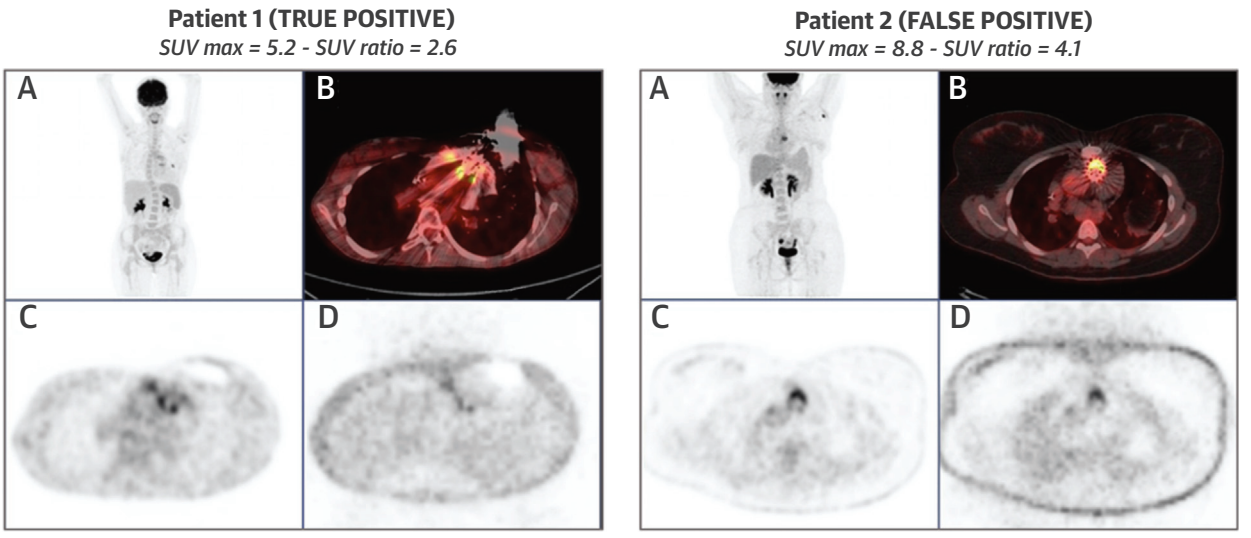
TABLE 7 Comparison of True Negatives and False Positives on Factors That May Affect PET/CT Specificity

	True Negatives (n = 8)	False Positives (n = 3)
Age, y	32.3 (20.1-38.3)	23.2 (18.9-41.3)
Male	5 (62.5)	1 (33.3)
Time from surgery to PET/CT, d	1,502 (725-2,183)	429 (228-1,574)
Homograft	0	0
BJV conduit/prosthesis	7 (87.5)	2 (66.7)
Fever	3 (37.5)	3 (100.0)
CRP,[a] mg/L	5 (3-27)	8.5 (6-11)
Leukocytes,[a] G/L	7.2 (6.4-8.8)	5.2 (5.1-5.3)

Values are median (interquartile range) or n (%). [a]Values of biological parameters on the date of the PET/CT.

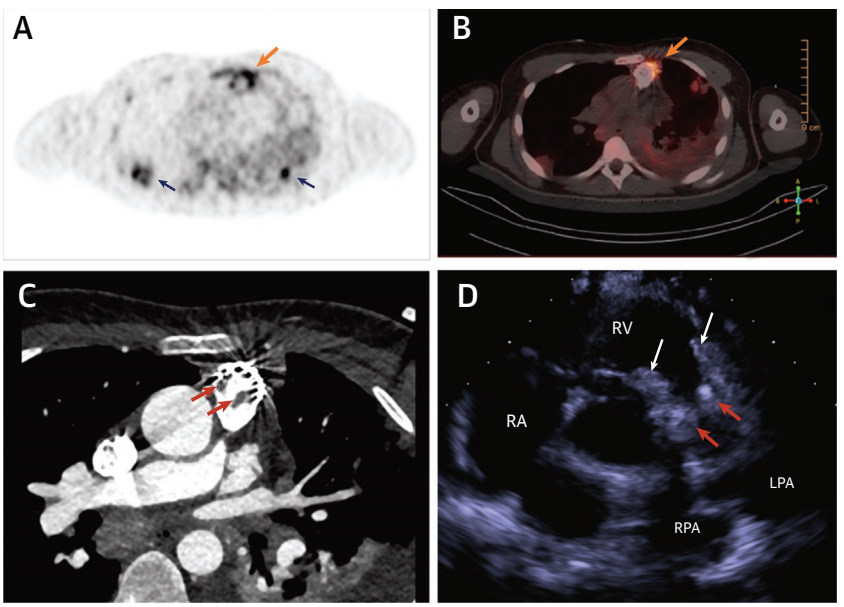
Abbreviations as in Tables 3 and 6.

FIGURE 3 True and False Positive PET/CT Examinations



(A) Maximum-intensity projection images, **(B)** PET/CT images fusion, **(C)** attenuation-corrected images, **(D)** attenuation-uncorrected images. SUV max is the maximal SUV in the targeted area (pulmonary prosthesis); SUV ratio is the ratio of prosthesis SUV max to background SUV (mediastinal SUV). SUV = standardized uptake value; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION Contribution of Multimodal Imaging in Diagnosis of Prosthetic Pulmonary Valve Infective Endocarditis



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A case of Melody valve endocarditis confirmed by TTE, cardiac computed tomography, and PET/computed tomography. Transaxial PET view **(A)** and fused PET/computed tomography view **(B)** show increased ^{18}F-fluorodeoxyglucose uptake in the anterior part of the Melody stent **(orange arrows)** and in several pulmonary foci related to septic embolism **(blue arrows in A)**. In that case, obstructive vegetations **(red arrows)** are also visualized on cardiac computed tomography **(C)** and on the TTE parasternal view **(D)**, filling the pulmonary valved stent **(white arrows)**. LPA = left pulmonary artery; PET = positron emission tomography; RPA = right pulmonary artery; TTE = transthoracic echocardiogram.

(CRP <40 mg/L) was predictive of a false negative examination (28). Accordingly, in our study, the CRP rate was lower in patients with a false negative PET/CT. Thus, physicians should be aware that PET/CT has to be performed early in the inflammation phase, and CRP levels could help guide the timing of PET/CT. Moreover, performing PET/CT early after the prosthesis implantation could favor false positives. Even though little evidence exists, many studies exclude these cases to avoid the risk of false-positive results, and the guideline authors even choose an arbitrary 3-month post-operative period to consider PET/CT as reliable (15). However, recent studies have challenged the relevance of this 3-month safety period and argue for a shorter waiting delay of 1 month (29). In our study, 1 of the false-positive cases can be explained by the very early realization of PET/CT compared with the implantation of the Melody valve (<1 month). However, our results also support the relevance of performing PET/CT before the 3-month postoperative period, but rather after the first month, because there were no false positives in the cases of PET performed between the first and third month.

STUDY LIMITATIONS. Although this study is the largest yet reported, our work has several limitations because of its retrospective nature. Despite the inevitable selection bias related to the fact that only patients who received PET/CT were included, our PPVE population is close to those described in literature. As expected in a retrospective multicenter work with no standardized PET/CT reports, some data were lacking, PET/CT analysis is mainly qualitative, and review of images by an independent expert nuclear physician was not always possible. This study produces a "real life" estimate of the diagnosis properties of the PET/CT. The lack of central blinded reviewing of each PET/CT examination by independent expert nuclear physicians brings another important bias to bear on the interpretation of the results and does not allow for inter-reader agreement information.

CONCLUSIONS

This is the first study assessing the diagnostic value of ^{18}F-FDG PET/CT in CHD patients with PPVE suspicion. We demonstrate a good diagnostic accuracy (sensitivity 79.1%; specificity 72.7%), with a particularly high positive predictive value of 91.9% and a favorable contribution of this imaging tool in the extracardiac work-up.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The ^{18}F-FDG PET/CT performances appear to be reliable in PPVE diagnosis; it should be systematically considered in case of PPVE suspicion. Including it in diagnostic criteria increases their sensitivity and contributes to improve clinical outcomes.

TRANSLATIONAL OUTLOOK: Future studies are needed to improve knowledge in PPVE diagnostic specificities: false negatives of PET/CT remain poorly understood, and a major objective would be to find ways to limit them. Quantitative analysis of PET/CT is also an interesting direction of study and could provide standardized results and diagnostic thresholds. Finally, increased transvalvular gradient seems to be a major criterion for IE in this population, but dedicated studies will be needed to confirm this.

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