Characterization of ^{18}F-Fluorodeoxyglucose Uptake Pattern in Noninfected Prosthetic Heart Valves

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Background—^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has been recently acknowledged as a diagnostic tool for prosthetic valve endocarditis, but its specificity is limited by uptake on noninfected valves. The objective of this study was to outline the main features of FDG uptake on PET/CT in patients with noninfected prosthetic heart valve (PHV).

Methods and Results—Our institution's PET/CT database was reviewed to identify patients with PHV, excluding those suspected of infection or who had received antibiotic treatment. PET indication, valve location, and type (biological/mechanical) and time from implantation were collected for each patient. Images with and without attenuation correction were considered for interpretation. The pattern of FDG uptake (absent, homogeneous, or heterogeneous) was recorded. Fifty-four PHVs (51 patients) were identified, including 32 biological valves. Indications for PET were oncology (n=26), suspicion of prosthetic valve endocarditis subsequently excluded (n=17), and history of vasculitis (n=11). A periprosthetic FDG uptake was present in 47 (87%) and 30 (56%) PHVs with and without attenuation correction, respectively, and the pattern was homogeneous in all but 4 (7%) and 3 (6%) PHVs, respectively. On quantitative analysis, maximum standardized uptake values was greater in mechanical than in biological valves (4.0 [2.4–8.0] versus 3.3 [2.1–6.1]; *P*=0.01) and in patients with vasculitis than in those referred for other indications. The uptake intensity did not differ before and 3 months after valve replacement.

Conclusions—Noninfected PHVs frequently display homogeneous FDG uptake, which remains steady over time. Caution is, therefore, needed when interpreting FDG PET/CT in suspected prosthetic valve endocarditis, with specific attention to uptake pattern. **(*Circ Cardiovasc Imaging*. 2017;10:e005585. DOI: 10.1161/CIRCIMAGING.116.005585.)**

Key Words: ^{18}F-FDG ■ infective endocarditis ■ prosthetic heart valve ■ PET/CT ■ vasculitis

Prosthetic valve endocarditis (PVE) represents 10% to 30% of all cases of endocarditis and occurs in 1% to 6% of patients with valve prosthesis.[1,2] It affects mechanical and bioprosthetic valves equally. PVE is associated with an in-hospital mortality rate of 20% to 40% and is even higher when the infecting agent is *Staphylococcus aureus*.[3–6] Such a high mortality rate is at least in part due to a delay in treatment initiation because of the difficulty in diagnosing infection on prosthetic valves. The direct evidence of vegetation or perivalvular complications of infection—a major criterion in the Duke–Li diagnostic criteria[7]—relies on echocardiography, but the presence of composite material generating acoustic shadowing results in inconclusive results in a substantial proportion of patients[8] and loss of diagnostic accuracy in PVE compared with native valve endocarditis, both for transthoracic and transesophageal echocardiography.[6]

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See Clinical Perspective

There is increasing evidence that FDG positron emission tomography (PET)/computed tomography (CT) may be useful in the management of infective endocarditis, both for detection of septic emboli[9–13] and for diagnosis of prosthetic valve infection.[14–16] A study showed that the sensitivity of the modified Duke criteria performed at admission was markedly increased when the presence of an abnormal FDG uptake was added as a major criterion.[14] Such evidence lead to the inclusion of the FDG PET/CT results as a major criterion of PVE in recently

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published European Society of Cardiology guidelines.[17] However, the latest American Heart Association guidelines on endocarditis state that more experience is needed to assess the diagnostic utility of FDG PET/CT.[18] It is acknowledged that a mild FDG uptake in the perivalvular area may occur in the absence of infection and may, therefore, be considered as a normal pattern, in particular, early after valve surgery.[17] In addition, the factors used to distinguish normal and abnormal patterns of FDG uptake are not standardized. To improve the diagnostic performance of FDG PET/CT, and particularly its specificity, it is critical to precisely describe FDG uptake in noninfected prosthetic heart valve (PHV).

We hypothesized that FDG uptake may be present in the perivalvular area in the absence of PVE. Secondary objectives were (1) to characterize the prevalence and pattern of FDG uptake in noninfected PHV, (2) to evaluate whether this uptake would disappear after a certain time interval after PHV implantation, and (3) to investigate the potential impact of patients' medical history on this pattern.

In the present study, we included patients with a history of cardiac valve replacement who were referred for PET/CT for a purpose unrelated to PVE. This approach allowed the recruitment of a large array of patients. We then analyzed the pattern and intensity of FDG uptake in the perivalvular area. Demographic, clinical, and biological parameters likely to affect FDG uptake, such as the type of valve, the time interval after implantation, and underlying disease, were also analyzed.

Methods

Study Population

The flowchart for patient selection is presented in Figure 1. The PET/CT database of our institution was reviewed for 24 months to identify patients with PHVs. They were divided into 3 groups according to the clinical indication for PET/CT referral: oncology (initial staging of cancer or suspicion of relapse), history of large vessel vasculitis (patients referred for follow-up without immunosuppressive therapy or under stable background therapy), and suspicion of PVE subsequently rejected. In the latter group, the Duke score was applied after ≥3-month follow-up or at the time of cardiac surgery. For all other patients, definite or possible infection during a follow-up of ≥3 months after the PET/CT scan, regardless of the location, was a criterion of exclusion. Patients who received antibiotic therapy, whatever the indication, in the period from 2 weeks before until 6 weeks after PET/CT scan were also excluded from the analysis. Patients with intense FDG physiological myocardial uptake, preventing analysis of the valve plane, were also excluded to comply with clinical practice in the setting of suspicion of PVE. To this purpose, all PET/CT scans were graded for myocardial uptake in a 3-level scale: absence of uptake when the FDG uptake on cardiac walls was lower than that of blood pool, faint or heterogeneous when uptake was the same level as the blood pool or greater but with areas with no uptake, and intense when left ventricular uptake was intense and homogeneous. Only the latter group of patients was excluded from further analysis. When sequential PET/CT had been performed in the same patient, only the first scan after valve replacement was considered so that each patient could only be analyzed once. For each patient, the following data were collected: age, sex, leukocyte count, C-reactive protein value, diabetic status, as well as those pertaining to the PHV—date of implantation, location (aortic or mitral), and type (biological or mechanical). The Institutional Review Board of Bichat Hospital approved this study, and all subjects gave informed consent for review of their records.

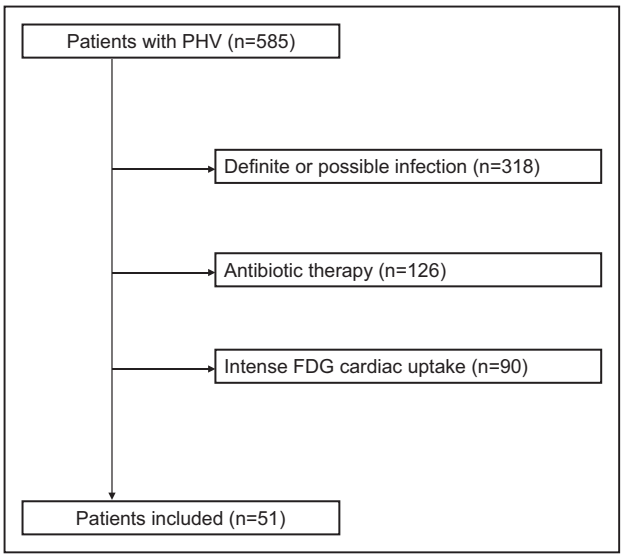

Figure 1. Study flow chart. PHV indicates prosthetic heart valve.

^{18}F-FDG PET/CT

Imaging Protocol

Patients were asked to fast for at least 6 hours before FDG injection. In diabetic patients, blood glucose plasma level had to be <12.0 mmol/L at the time of FDG injection. FDG was injected intravenously at a dose of 4 MBq/kg. PET/CT was performed 1 hour later on a PET/CT hybrid system (Discovery 690; General Electric Medical System, Buc, France). Imaging started with a nonenhanced, low-dose CT (120 kV, 80 mA) and was followed by whole-body PET acquisition in 3-dimensional mode, with an acquisition time of 3 minutes per bed position. PET images were reconstructed using 3-dimensional time-of-flight ordered-subsets expectation maximization with and without attenuation correction transaxial slices (256×256 matrix).

Interpretation Criteria

All cases were reviewed by an experienced nuclear medicine physician blinded to the type of cardiac valve and time interval from valve implantation. Image analysis was performed on ADW workstations (GE Medical Systems, Buc, France) and included both visual analysis and quantification of FDG uptake. First, the pattern of physiological myocardial FDG uptake was noted in 3 groups: absent, mild, or intense. Then the periprosthetic FDG uptake was qualitatively assessed on images that were corrected (AC) or not (NAC) for attenuation, on oblique views reoriented so that the plane of the slice coincided with the plane of the PHV, and quoted as (1) absent; (2) homogeneous when the uptake was diffuse around the PHV ring without focal enhancement; (3) heterogeneous when the uptake was either focal or diffuse with a focal enhancement (Figure 2). The perivalvular FDG uptake (perivalvular maximum standardized uptake value [SUV-V]) was measured on the same reoriented AC views to draw regions of interest in the plane of the valve. Planar circular regions of interest encompassing the perivalvular area were drawn on 3 adjacent slices, and the maximum standardized uptake values (SUVmax) of each slice were averaged as previously reported.[14–16] For the purpose of normalization of FDG intensity and to provide measurements comparable with previous publications on this topic,[14–16] the mean SUV in blood pool (SUV-B) was measured by manually positioning a 3-dimensional volume of interest in the right atrial cavity (avoiding atrial walls). The prosthetic valve-to-background ratio was calculated as SUV-V/SUV-B. Because in patients with a history of vasculitis, the FDG uptake in the aorta may have confounded the perivalvular assessment of PHV in aortic position, we also quantified FDG uptake in the ascending aorta. To that purpose, planar circular regions of interest encompassing the ascending aorta were drawn on adjacent slices, and the maximum standardized uptake value was referred to as SUV-aorta. The prosthetic aorta-to-background ratio was calculated as SUV-aorta/SUV-B.

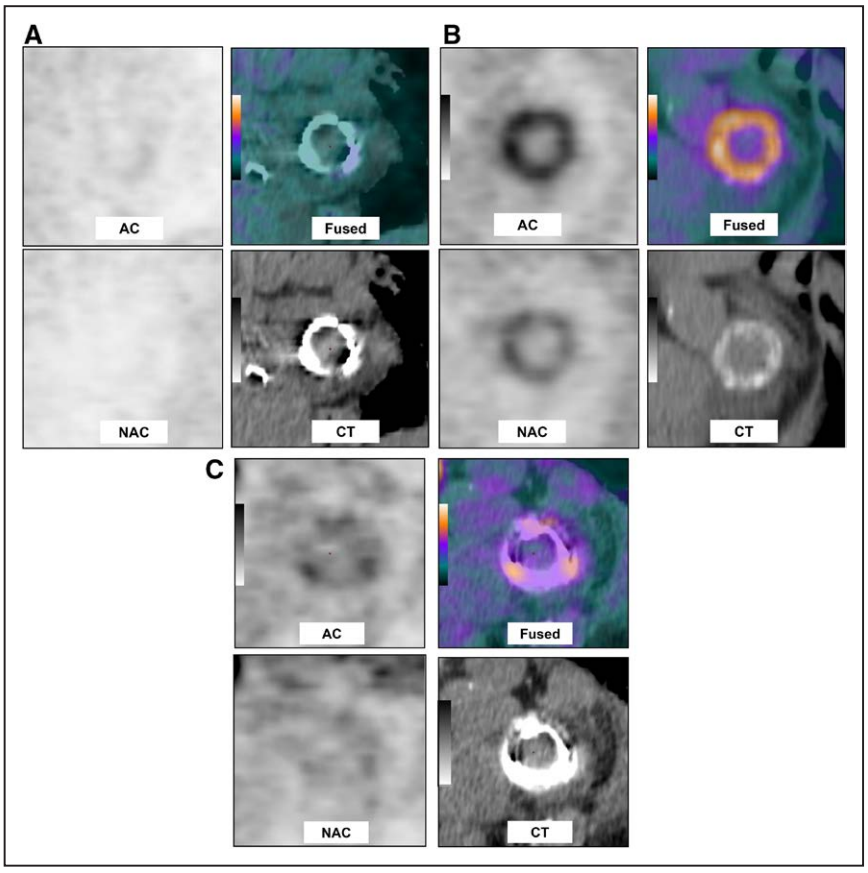

Figure 2. Examples of ^{18}F-FDG perivalvular uptake in noninfected patients. Reoriented (oblique) views in the plane of valve showing (**A**) absence of uptake in a 38-year-old woman with a biological prosthetic heart valve (PHV) implanted 3 years before for the indication of IE, who underwent FDG PET/CT in the work-up of lung cancer; (**B**) intense and homogeneous uptake in a 58-year-old woman with a biological PHV implanted 8 years before for the indication of aortic regurgitation because of infective endocarditis; (**C**) heterogeneous uptake in an 83-year-old female implanted with a biological PHV for severe mitral regurgitation 5 weeks before undergoing FGD PET/CT in the setting of fever with increased C-reactive protein level (48 mg/L). After 6-month follow-up without antibiotic therapy, no event occurred. The focal enhancement of the FDG uptake corresponds to the metallic stent posts of the valve. AC indicates attenuation-corrected images; CT, computed tomography; IE, infective endocarditis; NAC, non attenuation-corrected images; and PET, positron emission tomography.

Statistical Analysis

Statistical analysis was performed using the R software (version R.3.2.2; the R Foundation). Continuous variables were expressed by median and range. Categorical variables were expressed by their percentage. Comparisons across referral indication groups were performed using Fisher exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Comparisons by valve type or valve position were performed using Fisher exact test for categorical variables and either the *t* test or Mann–Whitney test for continuous variables. The relationship between SUV-V (or SUV-V/SUV-B) and time interval after valve implantation was expressed using Pearson's correlation coefficient. Comparisons of SUV-V and SUV-V/SUV-B between the 3 referral groups were performed using analysis of variance. Multiple linear regression analysis was used to investigate the relationships between SUV-V or SUV-V/SUV/B and variables related to the patients or the valves (valve type, valve position, and delay after implantation). A value of $P<0.05$ was considered significant.

The reproducibility of qualitative and quantitative assessment of perivalvular FDG uptake was checked by 2 experienced observers (Drs Mathieu and Rouzet) in patients included during the first 12 months of the study (n=36). The intraobserver and interobserver agreement of perivalvular uptake pattern (absent, homogeneous, or heterogeneous) was assessed by weighted Kappa coefficient, and the agreement of perivalvular FDG uptake intensity (SUV-V and SUV-V/SUV-B ratio) was expressed by Bland–Altman plot and compared using the intraclass correlation coefficient.

Results

Study Population

Among 585 patients with a PHV identified during the screening period, 51 met the inclusion criteria (Figure 1), with a total of 54 prosthetic valves. The selected patient characteristics are presented in Table 1. Out of 25 patients referred for oncological indication, most of them were investigated in the setting of initial staging of suspected (n=11) or proven (n=9) cancer. They had not had previous chemotherapy or radiotherapy when they underwent the PET/CT scan. Five additional patients were investigated for suspicion of cancer relapse. In this latter group, none had a history of radiotherapy involving the chest, and they received the last chemotherapy treatment at least 12 months before the PET/CT scan. After a follow-up of ≥3 months (median, 5 months; range, 3–12), none developed PVE. Out of 11 patients with a history of large vessel vasculitis, 3 presented with Takayasu disease, 3 with giant cell arteritis, 2 with Behcet disease, and 3 with other vasculitis. Among them, 5 were under stable background immunosuppressive therapy when they underwent the scan. After a follow-up of ≥3 months (median, 12 months; range, 3–12), none developed PVE. The main characteristics of the 15 patients referred for suspicion of PVE are presented in Table 2. Briefly, the suspicion was raised by either the occurrence of fever or an abnormal finding on echocardiography. The diagnosis of PVE had been ruled out by a diagnosis of rejected endocarditis as assessed by the Duke classification after follow-up in all patients. Three of them underwent valve replacement during the month after the PET scan, and the pathological analysis of the valve sample led to a conclusion of bioprosthesis degeneration in 2 patients and thrombus in 1 patient. One patient underwent heart transplant for advanced heart failure 3 months after the PET/CT scan without evidence of PVE at histological examination. In the 11 remaining patients, after a

Table 1. Selected Characteristics of the 51 Patients Included in the Study

	Overall Population (n=51)	Oncology (n=25)	Suspected Infection (n=15)	Vasculitis (n=11)	*P* Value
Age, y	66 (25–85)	70 (39–82)	66 (35–85)	55 (25–85)	0.02
Male sex, n (%)	29 (57)	19 (76)	4 (27)	6 (55)	0.01
Leukocyte count, 10^9/L	7.27 (4.60–33.92)	7.29 (4.60–33.92)	6.29 (4.77–11.61)	6.98 (5.76–9.60)	0.8
CRP value, mg/L	10 (3–213)	11.5 (3–213)	10 (3–169)	7 (3–117)	0.4
Glycemia,* mmol/L	5.8 (1.8–11.3)	6.0 (3.3–11.3)	5.6 (1.8–9.1)	5.6 (4.1–6.7)	0.8

Continuous variables are expressed as median (range). CRP indicates C-reactive protein.
*At the time of ^{18}FDG injection.

follow-up of >3 months (median, 6 months; range, 3 to 12), an alternative diagnosis was found in 4 patients, and no event occurred in 7 patients. No patients were lost to follow-up. It is noteworthy that most patients included in the study presented biological signs of inflammation with high values of leukocyte count and C-reactive protein, without significant difference according to referral indication (Table 1).

Valve characteristics are detailed in Table 3. The prosthetic valves were mostly biological (59%) and in aortic position (65%). The time interval between valve implantation and PET/CT ranged from 9 days to 25 years and was not statistically different between groups based on referral indication (Table 3). However, patients with biological valves were investigated earlier after implantation than those with mechanical valves (median, 3.6 versus 7.8 years; P=0.004). Fifteen patients were investigated <3 months after valve implantation, mainly with biological PHV (Table 4).

Periprosthetic FDG Uptake Pattern and Intensity

FDG uptake pattern and intensity are detailed in Tables 4 and 5. On visual analysis, FDG uptake was detectable in the periprosthetic area more frequently on AC images than on NAC images (87% versus 56%; P=0.0005) and with mechanical prosthesis than with biological ones (Table 4). The uptake was homogeneous in most cases (Table 4) both on AC and NAC images (Figure 2). Accordingly, in the overall population,

Table 2. Main Characteristics of Patients With Suspected Prosthetic Valve Endocarditis

Valve Position/Type	Time Interval After Valve Replacement, months	Symptoms/Signs	Echocardiography	FU Duration, months	Event	Final Diagnosis
Aortic/Biol	3	Fever	Normal	3	None	No infection
Mitral/Biol	1	None	3-mm mass on mitral annulus	3	None	Suture thread
Mitral/Mecha	2	Fever	Normal	3	None	No infection
Mitral/Biol	1	None	Paraprosthetic leakage	3	Heart transplantation	No infection
Mitral/Biol	1	None	Paraprosthetic mass	1	Mitral valve replacement	Thrombus
Mitral/Biol	1	None	Mass attached to the valve leaflet	6	Regression under anticoagulant treatment	Thrombus
Mitral/Mecha	195	Fever	Normal	3	None	No infection
Aorta/Biol (homograft after aortic endocarditis)	206	Dyspnea	Pseudoaneurysm of the aortic annulus	1	Aortic and mitral valve replacement	Homograft degeneration
Aorta/Biol	40	Fever	Normal	6	None	No infection
Aorta/Biol	93	Dyspnea	Aortic valve leakage	1	Aortic valve replacement	Bioprosthesis degeneration
Aorta/Biol	47	Suspicion of mycotic aneurysm	Normal	12	None	No infection
Aorta/Biol	40	None	Thickening of the prosthetic valve leaflets	12	None	Early bioprosthesis degeneration
Aorta/Biol	7	Inflammatory syndrome	Normal	12	None	No infection
Mitral/Mecha	228	Dyspnea	Paravalvular regurgitation	6	None	No infection
Aorta/Biol	137	Congestive heart failure	Mass attached to the mitral annulus	12	None	Mitral annular calcification

The most recent valve surgery has been considered in the 2 patients who have 2 prosthetic valves. Biol indicates biological; FU, follow up; and Mecha, mechanical.

Table 3. Characteristics of the 54 Prosthetic Heart Valves (PHV) According to the Referral Indication in the 51 Patients*

	All PHV (n=54)	Oncology (n=26)	Suspected PVE (n=17)	Vasculitis (n=11)	*P* Value
Valve position, n (%)					
Aorta	35 (65)	17 (65)	10 (59)	8 (73)	0.8
Mitral	19 (35)	9 (35)	7 (41)	3 (27)	
Valve type, n (%)					
Biological	32 (59)	16 (62)	13 (76)	3 (27)	0.03
Mechanical	22 (41)	10 (38)	4 (24)	8 (73)	
Delay between valve implantation and imaging, days	1957 (9–9044)	2361 (9–9044)	2039 (25–6952)	786 (34–2335)	0.1

Continuous variables are expressed as median (range). PVE indicates prosthetic valve endocarditis.

*Three patients had 2 prosthetic valves (2 in the group suspected PVE and 1 in the group vasculitis), which were analyzed independently.

heterogeneous uptake was present in only 4 PHV (7%) on AC and 3 (6%) on NAC images (Table 4). Among the 4 patients presenting with a heterogeneous uptake on AC images, 3 had a mechanical prosthetic valve in aortic position, and the remaining patient had a biological prosthesis implanted for <3 months (Figure 2C). Interobserver and intraobserver agreement of qualitative assessment of periprosthetic FDG uptake assessed by weighted Kappa coefficient were 0.89 (95% confidence interval, 0.75–1.0).

Quantitative analysis using either SUVmax alone (SUV-V) or corrected for bloodpool activity (SUV-V/SUV-B ratio) further evidenced the higher uptake of mechanical compared with biological valves (Table 4). Interobserver agreement of quantitative assessment of periprosthetic FDG uptake was 0.99 (95% CI, 0.99–1.0 for SUV-V and 0.98 (95% CI, 0.96–0.99) for SUV-V/SUV-B ratio. The mean difference between operators was 0.03 (95% limit of agreement, −0.36; 0.31) for SUV-V and 0.02 (95% limit of agreement, −0.43; 0.47) for SUV-V/SUV-B ratio. Intraobserver agreement of quantitative assessment of periprosthetic FDG uptake was 0.99 (95% CI, 0.99–1.0) for SUV-V and 0.97 (95% CI, 0.95–0.99) for SUV-V/SUV-B ratio. The mean difference between the 2 sets of measurements was 0.01 (95% limit of agreement, −0.17; 0.18) for SUV-V and −0.02 (95% limit of agreement, −0.31; 0.27) for SUV-V/SUV-B ratio.

A subgroup analysis showed that patients referred for large vessel vasculitis presented higher uptake values compared with those referred for oncology or suspicion of PVE (Table 5), with a median SUV-V of 4.7 versus 3.3 and 3.5 and median SUV-V/SUV-B of 2.7 versus 1.9 and 1.8, respectively, (P<0.001 for both SUV-V and SUV-V/SUV-B). Of note, SUVmax of the ascending aorta or SUV-aorta/SUV-B was not significantly greater in patients with vasculitis (Table 5). Although more patients in this subgroup were implanted with a mechanical prosthesis, the association remained significant by multivariate linear regression analysis (P=0.001 for both SUV-V and SUV-V/SUV-B). After exclusion of patients with vasculitis, FDG uptake was detectable in the periprosthetic

Table 4. FDG Uptake Pattern and Intensity According to Prosthetic Valve Type and Position

		Valve Type			Valve Position		
	All PHV (n=54)	Biological (n=32)	Mechanical (n=22)	*P* Value	Aortic (n=35)	Mitral (n=19)	*P* Value
Time from implantation, n (%)							
<3 mo	15 (28)	11 (34)	4 (18)	0.06	7 (20)	8 (42)	0.1
>3 mo and <1 y	4 (7)	4 (13)	0 (0)		4 (11)	0 (0)	
>1 y	35 (65)	17 (53)	18 (82)		24 (69)	11 (58)	
Periprosthetic FDG uptake pattern							
Absence of uptake, n (%)							
AC	7 (13)	6 (19)	1 (4.5)	0.2	5 (14)	2 (11)	1
NAC	24 (44)	18 (56)	6 (27)	0.03	17 (49)	7 (37)	0.1
Homogeneous uptake, n (%)							
AC	43 (80)	25 (78)	18 (82)	1	27 (77)	16 (84)	0.8
NAC	27 (50)	13 (41)	14 (64)	0.2	16 (46)	11 (58)	0.6
Heterogeneous uptake, n (%)							
AC	4 (7)	1 (3)	3 (13)	0.3	3 (9)	1 (5)	1
NAC	3 (6)	1 (3)	2 (9)	0.6	2 (6)	1 (5)	1
Periprosthetic FDG uptake intensity							
SUV-V	3.5 (2.1–8.0)	3.3 (2.1–6.1)	4.0 (2.4–8.0)	0.01	3.6 (2.1–8.0)	3.5 (2.4–6.1)	0.8
SUV-B	1.8 (1.0–2.8)	1.8 (1.0–2.8)	1.8 (1.0–2.7)	0.9	1.8 (1.0–2.7)	1.8 (1.0–2.8)	0.8
SUV-V/SUV-B	2.0 (1.3–6.6)	1.9 (1.3–5.1)	2.1 (1.4–6.6)	0.03	1.9 (1.3–6.6)	2.0 (1.4–5.1)	0.8

Continuous variables are expressed as median (range). AC indicates attenuation-corrected images; NAC, nonattenuation-corrected images; PHV, prosthetic heart valve; SUV-B, mean SUV in blood pool; and SUV-V, perivalvular SUVmax.

Table 5. FDG Uptake Pattern and Intensity According to Referral Indication

	Oncology (n=26)	Suspected PVE (n=17)	Vasculitis (n=11)	*P* Value
Qualitative assessment of the perivalvular FDG uptake				
AC				
Absence of uptake, n (%)	3 (11.5)	4 (23.5)	0 (0)	0.5
Homogeneous uptake, n (%)	21 (81)	12 (70.5)	10 (91)	
Heterogeneous uptake, n (%)	2 (7.5)	1 (6)	1 (9)	
NAC				
Absence of uptake, n (%)	13 (50)	9 (53)	2 (18)	0.4
Homogeneous uptake, n (%)	12 (46)	7 (41)	8 (73)	
Heterogeneous uptake, n (%)	1 (4)	1 (6)	1 (9)	
Quantitative assessment of the perivalvular FDG uptake				
SUV-V	3.3 (2.1–5.7)	3.5 (2.1–4.7)	4.7 (3.0–8.0)	<0.001
SUV-B	1.8 (1.0–2.7)	1.9 (1.3–2.8)	1.8 (1.5–2.2)	0.5
SUV-V/SUV-B	1.9 (1.4–3.8)	1.8 (1.3–2.3)	3.1 (1.6–3.9)	<0.001
FDG uptake in the ascending aorta				
SUV-aorta	2.7 (2.0–3.6)	2.9 (1.3–3.5)	2.5 (2.1–3.7)	0.4
SUV-aorta/SUV-B	1.4 (1.2–1.9)	1.5 (1.2–1.9)	1.5 (1.2–1.7)	0.8

Continuous variables are expressed as median (range). AC indicates attenuation-corrected images; NAC, non attenuation-corrected images; PVE, prosthetic valve endocarditis; SUV-B, mean standardized uptake values in blood pool; and SUV-V, perivalvular maximum standardized uptake values.

area in 36 (84%) PHV with AC and in 22 (51%) PHV without AC in the remaining study population (in comparison to patients with vasculitis; *P*=0.3 and 0.09, respectively); the median SUV-V was 3.5 (2.1–5.7), and the median SUV-V/SUV-B ratio was 1.9 (1.3–3.8). No significant difference in SUV-V or SUV-V/SUV-B ratio was found according to sex (*P*=0.12), blood glucose level at the time of FDG injection (*P*=0.48), or diabetic status (*P*=0.08).

Of note, both qualitative and quantitative analysis of perivalvular FDG uptake yielded similar results whatever the valve position (Table 4), suggesting that the close proximity of FDG physiological faint uptake by the myocardium and PHV in mitral position did not affect the evaluation of the pattern or the SUV of the valve.

Relationship Between FDG Uptake and Time From Implantation

On visual analysis, FDG uptake was detectable in the periprosthetic area more frequently in PHV implanted <3 months prior to the analysis (n=15) than in others, but the difference was not significant (respectively, 93% versus 85%; *P*=0.7 with attenuation correction; and 67% versus 51%, *P*=0.4 without attenuation correction). Likewise, there was no significant difference in SUV-V or in the SUV-V/SUV-B ratio between PHV implanted for <3 months and those that had been in place for longer (SUV-V, 3.5 [2.4–5.8] versus 3.5 [2.1–8.0]; *P*=0.5 and SUV-V/SUV-B ratio, 1.9 [1.4–3.9] versus 2.0 [1.3–6.6]; *P*=0.5). In addition, SUV-V was not correlated with time from implantation (*R*=−0.07; *P*=0.60; Figure 3). A subgroup analysis showed that SUV-V in biological valves was weakly and inversely correlated with time (*R*=−0.36; *P*=0.04), but this was not the case for mechanical valves (*R*=−0.19; *P*=0.40).

Discussion

The present study shows that noninfected PHV often display a homogeneous FDG uptake that is independent of the time interval between valve implantation and imaging. In addition, the intensity of the FDG uptake seems to be greater in patients with a history of vasculitis.

In the setting of PVE, FDG PET/CT proved to be helpful by providing evidence of periprosthetic hypermetabolism when echocardiography is inconclusive.[14,15] It is generally considered that perivalvular uptake is increased during the few months after valve replacement. Indeed, most of the false-positive scans in our previous series occurred in patients with a prosthetic valve implanted <2 months before undergoing FDG PET/CT.[15] For this reason, Saby et al[14] did not include patients investigated during the first month after valve implantation, and European Society of Cardiology recommendations do not consider PET/CT results during the first 3 months after implantation.[17] In the present study, the mean SUVmax was not statistically different whether prostheses were implanted before or after the 3-month threshold. Only a weak correlation between the time from valve replacement and the intensity of FDG uptake could be evidenced in the subgroup of patients with a biological prosthesis. Consequently, the presence of a perivalvular uptake should be interpreted with great caution even after the first 3 postoperative months.

The periprosthetic FDG uptake was present on visual analysis in most patients on AC images. This uptake was somewhat lower on NAC images, suggesting the occurrence of overcorrection artifacts[19] related to the presence of composite components of PHV in some patients. Such artifacts have been well investigated in cardiac-implanted electronic devices,[20,21] but much less in PHV. The greater values of SUVmax and valve-to-background ratio calculated in the presence of a mechanical valve also support the role of AC because more composite material is present. However, FDG uptake was also present in 56% of patients on noncorrected images. Based on data obtained in patients with a definite or rejected diagnosis of PVE, our group[15] and others[16] suggested cutoff values of SUVmax and uptake ratios designed to help discriminate between infected and noninfected PHV. In their series of patients suspected of PVE or cardiac implantable electronic devices infection, Pizzi et al[16] report a specificity of 79% when SUVmax was ≥3.7 and 100% when SUVmax was ≥6.9. In the present series of patients free from infection, SUVmax ranged from 2 to 5 in most cases and ≤8 in the subgroup of patients with vascular disease. The comparison of the FDG uptake level with previous reports in patients with PVE[14–16] shows that even if mean values are greater in patients with definite PVE, there is no threshold that allows reliable differentiation between infected and noninfected PHV because of a wide

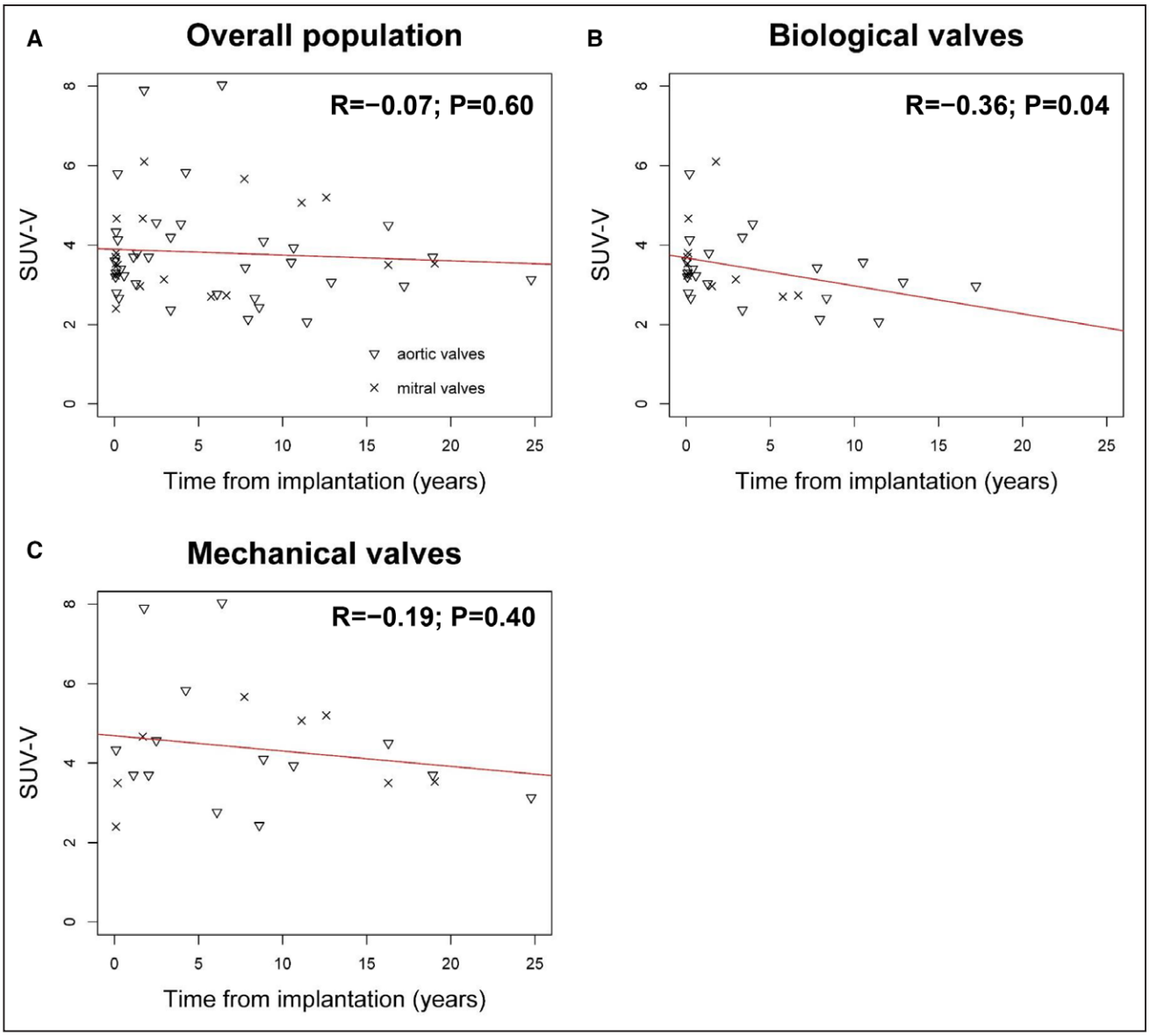

Figure 3. Relationship between perivalvular maximum standardized uptake values (SUV-V) and time from implantation in (**A**) the overall population, (**B**) the subgroup of biological prosthesis (n=32), and (**C**) the subgroup of mechanical prosthesis (n=22).

overlap between values. In the present study, a greater FDG uptake was evidenced in patients with a history of vasculitis but without evidence of active disease. The increased level of FDG uptake was possibly related to the presence of a baseline arterial inflammation in this specific subgroup of patients, and the discrimination between infection and mere inflammation should be even more careful in this subgroup of patients to avoid inappropriate redo surgery.

A homogenous uptake pattern present on visual analysis in almost all cases suggests that this feature was associated with the physiological scarring process around PHVs. Early after valvular implantation, migration and proliferation of inflammatory cells, myofibroblasts, and capillary endothelial cells are triggered by the host tissue reaction,[22] which is likely to provoke an increased FDG uptake. Thereafter, the progression of the healing process leads to the formation of a fibrous cuff with increasing amounts of collagen and re-endothelialization of the sewing ring.[22] The persistence of FDG uptake in the periprosthetic area, even on noncorrected images, is likely to account for the persistence of a remodeling process around the sewing ring. The variability of periprosthetic FDG uptake in the absence of infection may be related to the variability of the fibrous tissue ingrowth on the sewing ring. Endothelialization of the sewing ring is a physiological healing process that varies from one patient to another and may even consist in a marked fibroblastic proliferation with chronic inflammatory features, leading to obstructive pannus in the most severe cases.[23] A similar pattern has been reported by Keidar et al[24] in the setting of vascular prosthesis. In their study, the authors showed that FDG uptake could remain intense over time in synthetic prosthesis, whereas it decreased in native vein grafts. Because the sewing ring of PHV and vascular grafts are made of similar synthetic biomaterial, it is likely that a common reaction occurs in both settings.

With regards to the recently issued European Society of Cardiology guidelines on infective endocarditis,[17] where the presence of abnormal activity around a PHV is considered as a major criterion of infective endocarditis, the interpretation of FDG PET should be performed carefully. In particular, the pattern of faint or homogeneous perivalvular uptake should not be considered abnormal, regardless of the delay from prosthesis implantation. The present findings also highlight the fact that diagnostic criteria should not be a substitute for the clinical judgment of the endocarditis team, as stated in the guidelines.

Limitations of the Study

Because of the retrospective nature of patients' enrollment, they did not undergo the specific high-fat low-carbohydrate diet followed by 12 hours fasting intended to minimize FDG cardiac uptake. As a consequence, a substantial proportion presented an intense myocardial FDG uptake. Because they were not representative of the target population, we excluded those patients from analysis so that the results of the study may apply to patients referred for suspicion of PVE who undertook the appropriate diet. In the remaining study population, the spectrum of FDG cardiac uptake pattern was comparable to that of the population of our previous series with a low or mild uptake in most patients.[15] Likewise, the mean values of SUVmax in patients without PVE in our previous series and in the present study population were in the same range. Hence, we can infer that the study population is representative of the general population undergoing FDG PET in the setting of suspicion of PVE as regards metabolic status. The inclusion criteria did not allow to formally exclude ongoing vasculitis that may have represented a confounding factor, leading to an overestimation of perivalvular FDG uptake in this subgroup. Although we ruled out any contribution of underlying aortic FDG uptake by determining that the signal in the ascending aorta was not significantly greater in patients with vasculitis compared with the rest of the study population, this finding should be further substantiated by dedicated studies.

Conclusions

Noninfected PHVs frequently display homogeneous FDG uptake in the perivalvular area on PET/CT. This pattern is present years after valve implantation and should not be considered, per se, as a marker of prosthetic material infection. In addition, such FDG uptake was slightly greater in mechanical versus biological prosthesis and in patients with vasculitis. Caution is, therefore, needed when interpreting FDG PET/CT in suspected PVE, and special attention should be paid to the uptake pattern. Finally, these findings highlight the need to integrate the results of FDG PET/CT in the clinical context.

Disclosures

None.

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CLINICAL PERSPECTIVE

There is increasing evidence that fluorodeoxyglucose (FDG) positron emission tomography/computed tomography may be useful in infective endocarditis management, both for detection of septic emboli and for diagnosis of prosthetic valve endocarditis when echocardiography is inconclusive. Such evidences lead to inclusion of the FDG positron emission tomography/computed tomography result as a major criterion of prosthetic valve endocarditis in European Society of Cardiology guidelines, whereas the last American Heart Association recommendations on endocarditis state that more experience is needed to assess the diagnostic utility of FDG positron emission tomography/computed tomography. The present study shows that noninfected prosthetic heart valves often display a homogeneous FDG uptake. This pattern is present even years after valve implantation and should not be considered, per se, as a marker of prosthetic material infection. In addition, the intensity of the FDG uptake did not decrease according to time from valve surgery and seemed to be greater in patients with a history of vasculitis.

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Characterization of ^{18}F-Fluorodeoxyglucose Uptake Pattern in Noninfected Prosthetic Heart Valves

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