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18-Fluoro-2-deoxyglucose positron emission tomography–computed tomography: an additional tool in the diagnosis of prosthetic valve endocarditis☆

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SUMMARY

Objectives: To evaluate the role of 18-fluoro-2-deoxyglucose positron emission tomography–computed tomography (^{18}F-FDG-PET–CT) in the diagnosis of infectious endocarditis (IE).
Methods: We retrospectively examined 27 consecutive patients who were admitted to the Infectious Diseases Department of Tor Vergata University Hospital between 2009 and 2013 with a suspicion of IE. The final IE diagnosis was defined according to the modified Duke criteria, and the microbiological and diagnostic results were collected for each patient.
Results: Twenty out of 27 patients had a suspected prosthetic valve endocarditis (PVE) and seven had a suspected native valve endocarditis (NVE). Twenty-five out of 27 patients (92%) had a confirmed diagnosis of IE (18/25 PVE and 7/25 NVE); 16 had a positive echocardiography evaluation and 16 had positive ^{18}F-FDG-PET–CT findings. Echocardiography showed a higher sensitivity as a diagnostic tool for the detection of IE compared to ^{18}F-FDG-PET–CT (80% vs. 55%). However, a greater number of PVE had positive ^{18}F-FDG-PET–CT results compared to those with positive echocardiography findings (11/13 vs. 9/13), and overall 89% (16/18) of confirmed PVE resulted ^{18}F-FDG-PET–CT positive. Analyzing only the cases who underwent transoesophageal echocardiography, ^{18}F-FDG-PET–CT showed a sensitivity of 85% in PVE (vs. 69% for echocardiography and 77% for the Duke criteria). All seven patients with NVE had a positive echocardiography and negative ^{18}F-FDG-PET–CT findings ($p < 0.001$).
Conclusions: The results of this study further highlight the limitations of echocardiography in the diagnosis of PVE and the potential advantages of ^{18}F-FDG-PET–CT in these cases.

1. Introduction

Infective endocarditis (IE) continues to be an important medical issue. The incidence of IE ranges from 3 to 10 episodes/100 000 person-years, and the risk of developing IE increases dramatically with age (14.5 episodes/100 000 person-years for patients aged 70–80 years).[1,2] Over the past 30 years, neither the incidence nor the associated mortality has decreased, despite major advances in both diagnostic and therapeutic procedures. New predisposing factors have been identified, such as valve prostheses, degenerative valve sclerosis, and intravenous drug abuse.[1]

Prosthetic valve endocarditis (PVE) represents an extremely serious medical condition with a potentially deleterious outcome. PVE accounts for 10–30% of all cases of IE and occurs in 1–6% of patients with valve prostheses, with an incidence of 0.3–1.2% per patient/year.[2] A definitive IE diagnosis is based on the revised Duke criteria[3] and is generally more difficult for prosthetic than native valves,[4] as transthoracic echocardiography (TTE) has limited diagnostic power on prosthetic valves. Transoesophageal echocardiography (TEE) is essential in patients suspected for PVE,

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otherwise both TTE and TEE are limited by their dependence on the individual patient's morphology, instrumental settings, transducer position, operator, and artefacts from heavy valve calcifications and metallic prosthetic valves through acoustic shadowing. Therefore, if an initial echocardiography is negative, repeated TEE examinations are recommended in cases of clinical suspicion.[5,6] The question of whether performing TTE prior to TEE is necessary in the evaluation of suspected prosthetic valve vegetations is a difficult one. Guidelines provided by the American Heart Association, American College of Cardiology, and American Society of Echocardiography in 2003,[7] stated that sequential examinations starting with TTE is the preferred approach given the essential information on cardiac function and haemodynamics provided by TTE. However, particularly in the case of PVE, protocols in which TTE is ordered first may subject patients to unnecessary delays in diagnosis as well as increased overall costs, and also the results of this test are more frequently negative for PVE.[8]

18-Fluoro-2-deoxyglucose positron emission tomography–computed tomography (^{18}F-FDG-PET–CT) (fluorodeoxyglucose labelled with fluorine-18) is a well-recognized imaging tool that is most often used in oncology, but also in infectious diseases, vasculitis, cardiology, and neurology disorders;[9–12] increased levels of glucose are detected in granulocytes and monocytes. Emerging data suggest a role for ^{18}F-FDG-PET–CT in the diagnosis of endocarditis and endovascular graft and pacing system infections when conventional diagnostic tools have failed.[13–16]

The aim of this study was to evaluate the diagnostic efficacy of ^{18}F-FDG-PET–CT in native valve endocarditis (NVE) and PVE in a group of patients referred to our department with a suspicion of IE during the period 2008–2013.

2. Methods

2.1. Patients

Between January 2008 and October 2013, 27 consecutive patients were admitted to the Infectious Disease Department with a suspicion of IE. On admission, the evaluation of possible and definite IE cases was based on the clinical and/or pathological modified Duke criteria.[3] The final IE diagnosis was defined according to the modified Duke criteria and the microbiological and diagnostic results collected from each patient. The assessment of individual cases on the basis of the above criteria allowed us to confirm or reject the diagnosis of IE.

All of the patients underwent physical examinations, laboratory investigations, culture tests, and additional diagnostic procedures, including chest X-ray, abdominal ultrasound, and TTE. As a result of technical problems, intolerance, or patient refusal, TEE examination was limited to only 11 patients. All of the accepted patients underwent ^{18}F-FDG-PET–CT at admission, a median of 4 days (range 3–8 days) after the start of antibiotic therapy. ^{18}F-FDG-PET–CT was used as an additional tool to confirm the diagnosis of IE, to evaluate peri-valve extensions and early peripheral embolisms, or to rule out other infectious foci, and was never used alone to assess the clinical management of the patients.

Late PVE was defined as an infection that presented at >12 months after heart surgery, and early PVE as an infection that presented at <12 months after surgery.

Demographic, clinical, microbiological, and treatment data were collected retrospectively. The ethics committee of Tor Vergata University Hospital approved this study.

2.2. ^{18}F-FDG-PET–CT

All patients underwent ^{18}F-FDG-PET–CT in the resting state after eating a meal rich in fat and low in carbohydrates to reduce the physiological uptake of FDG in the myocardium.[17] The test was performed after a 6-h fasting period. Glycaemia was determined to be ≤120 mg/dl at the time of the study. One hour after the intravenous injection of 4 MBq/kg ^{18}F-FDG, a low-dose whole-body CT scan from the mid-thigh to the vertex was acquired using a Discovery VCT PET/CT (GE Healthcare, Milwaukee, WI, USA). Once the CT imaging was completed, PET acquisition was performed in the three-dimensional mode, and the data were reconstructed using the iterative method (algorithm OSEM); the CT data were used for attenuation correction.

2.3. Interpretation of ^{18}F-FDG-PET–CT

The cardiac images were interpreted independently by two nuclear medicine physicians who were blinded to the clinical data and other imaging studies. In two cases where the two physicians disagreed on a diagnosis, consensus was reached via a third physician. In patients with suspected NVE, any increase in FDG uptake in or around the heart valves outside the myocardium was considered abnormal. In patients with suspected PVE, the analysis was performed on both the attenuation-corrected and non-attenuation-corrected images, and the presence of hotspots in the prosthetic and periprosthetic areas was considered abnormal (Figures 1 and 2).

2.4. Statistical analysis

This should be considered a retrospective and observational study. Continuous variables are expressed as the mean value. Categorical data are expressed as numbers with percentages. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using the final diagnoses of confirmed NVE or PVE and the rejected NVE or PVE as the outcomes. The sensitivity, specificity, NPV, and PPV of the Duke criteria, echocardiography (TTE and TEE), and ^{18}F-FDG-PET–CT were calculated based on the final diagnosis of IE using SPSS

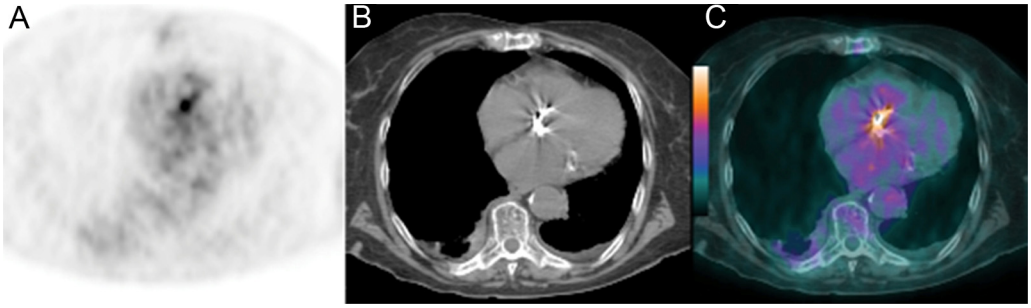

Figure 1. Transverse images from an 83-year-old woman with PVE: (A) ^{18}F-FDG-PET–CT; (B) CT; (C) integrated ^{18}F-FDG-PET–CT. High FDG uptake was observed at the level of the aortic prosthesis.

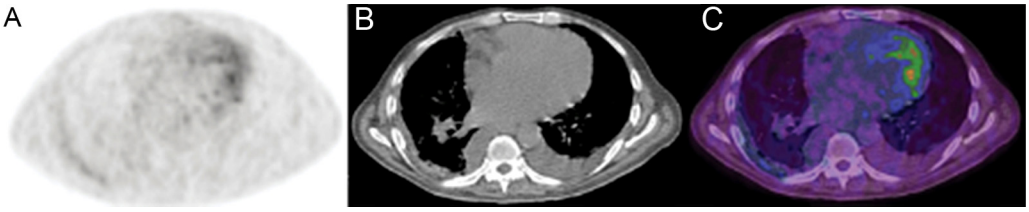

Figure 2. Transverse images from a 63-year-old man with NVE: (A) ^{18}F-FDG-PET–CT; (B) CT; (C) integrated ^{18}F-FDG-PET–CT. PET/CT detected no ^{18}F-FDG accumulation in the aortic valve vegetation, which was detected by TEE.

16.0 software (SPSS Inc., Chicago, IL, USA). All of the tests were two-sided. A p-value of <0.05 was considered significant.

3. Results

Table 1 shows the characteristics of the 27 patients enrolled in the study, 20 of whom had a prosthetic valve and seven of whom had a native valve. The majority of the patients were men (74%, 20/27), and the mean age was 63 years (range 41–83 years). At the final evaluation, the IE diagnosis was confirmed in 25 of the 27 patients (92%), and these patients were treated with a standard course of antibiotics in accordance with international guidelines.[1,2] In two cases (patients 17 and 18) with a possible IE diagnosis according to the modified Duke criteria at admission, the final IE diagnosis was rejected. Of the 25 patients with a confirmed IE final diagnosis, 18 (72%) had PVE (16 aortic and two mitral prosthetic valves). Eight patients (44.4%) had an early infection, with a mean time to onset from surgery of 5 months, whereas 10 patients (55.5%) had a late infection, with a mean time to onset from surgery of 12 months. Seven (28%) out of 25 patients had NVE.

All 20 PVE patients underwent TTE at the initial diagnostic evaluation and only nine patients were subsequently evaluated by TEE. In five out of 11 patients (patients 10, 12, 14, 16, and 19) not evaluated with TEE, the TTE resulted positive for IE; the remaining six patients refused or did not tolerate the examination. Five of these (patients 1, 3, 4, 7, and 20) were confirmed with IE at the final evaluation and were treated successfully with antibiotics according to the procedures and time limits established in international guidelines. For the sixth patient (patient 18), the diagnosis of IE was rejected.

Only two out of nine patients who underwent TEE (patients 9 and 15) the exam provide additional diagnostic information to TTE. Seven out of the nine patients with positive TEE findings also had a positive ^{18}F-FDG-PET–CT result and had a confirmed IE diagnosis at the final evaluation. The other two patients, one with a positive and one with a negative TEE evaluation, had negative ^{18}F-FDG-PET–CT results. The last patient (patient 17) had a rejected IE final diagnosis. All patients with NVE had evidence of vegetations on TTE; TEE was done in only two cases, which confirmed TTE findings.

Due to persistent infections despite antibiotic treatment, valve replacements were needed in seven cases (four with PVE and three with NVE), and a valvuloplasty was needed in one case. A prolonged antibiotic course (6–12 months) was needed for 10 PVE cases in whom prosthetic valve replacement was not possible due to the high surgical risk. Valve infections were confirmed by biopsy' in two cases (patient 6 *Enterococcus faecalis*, and patient 10 *Candida parapsilosis*).

There were four in-hospital deaths (14%) due to complications of sepsis (Table 1; patients 1, 11, 16, and 24). The remaining 21 patients were treated successfully and were considered infection-free when screened at the scheduled follow-up.

The main presenting symptoms of suspected IE were fever of unknown origin (17/27, 62%), bacteraemia or sepsis (5/27, 18%), major vascular phenomena (3/27, 11%), vegetations (10/27, 37%), valvular or perivalvular damage (3/27, 11%) as determined by TTE, and dyspnoea and chest pain in one case.

In the 25 cases of confirmed IE, the causative microorganisms were coagulase-negative staphylococci in four cases, *Enterococcus faecalis* in six cases, *Streptococcus viridans* in four cases, *Candida parapsilosis* in two cases, methicillin-sensitive *Staphylococcus aureus* (MSSA) in two cases, *Pseudomonas aeruginosa* in two cases, methicillin-resistant *S. aureus* with reduced susceptibility to vancomycin (hetero-VISA) in one case, *Streptococcus bovis* in one case, and *Enterococcus spp* in one case (organism identified through molecular testing). Four patients had culture-negative IE; these patients were taking antibiotics at the time of clinical evaluation and tested negative for *Coxiella burnetii* serology (data not shown).

Table 2 shows a comparison of the revised Duke criteria evaluations, TTE or TEE echocardiogram findings, and ^{18}F-FDG-PET–CT scan results. The comparison of the different methods was conducted on only 22 out of the 27 subjects studied, considering only PVE patients with positive echocardiography evaluations and ruling out patients without a TEE evaluation. In this table, the sensitivity, specificity, PPV, and NPV for the overall studied patients (section A) and separately for the 15 patients with suspected PVE (section B) and the seven patients with NVE (section C) were reported according to the final diagnosis of confirmed or rejected IE.

In section A, according to the Duke criteria, only two patients with possible IE were not confirmed at the final evaluation (sensitivity 70%, specificity 100%, PPV 100%, and NPV 25%). At the echocardiography (TTE or TEE) evaluation, 16 out of 20 patients with confirmed IE had positive findings (sensitivity 80%, specificity 100%, PPV 100%, and NPV 33%). Finally, 11 out of 20 patients with a confirmed IE final diagnosis had positive ^{18}F-FDG-PET–CT results (sensitivity 55%, specificity 100%, PPV 100%, and NPV 18%). The diagnostic tool with the greatest sensitivity in detecting IE in the total studied population was echocardiography (80% vs. 70% for the revised Duke criteria and vs. 55% for ^{18}F-FDG-PET–CT).

In section B, 13 out of 15 patients with suspected PVE had a confirmed IE final diagnosis. Four of these patients had negative echocardiography results, and two of these patients had negative ^{18}F-FDG-PET–CT results. ^{18}F-FDG-PET–CT showed a sensitivity of 85% (vs. 69% for echocardiography and 77% for the revised Duke criteria). A greater number of patients with PVE had positive ^{18}F-FDG-PET–CT results compared to those with positive echocardiography findings (11/13 vs. 9/13).

In section C, all seven patients with NVE had positive echocardiography and negative ^{18}F-FDG-PET–CT findings ($p < 0.001$). The echocardiography findings had a sensitivity of 100% (vs. 57% for the revised Duke criteria).

4. Discussion

In this retrospective study of patients with suspected IE, echocardiography was shown to have the highest sensitivity (80%) as a diagnostic tool in evaluating the overall population. The ability

Table 1
Characteristics of the study population

No.	Sex, age	Medical history	Microbiological blood culture	Valve	Onset from surgery	Increased uptake of ^{18}F-FDG-PET–CT	TTE	TEE	Duke criteria	IE final diagnosis
1	M, 74 y	Persistent fever	*Candida parapsilosis*	Aortic and mitral prosthetic valve	7 y, late	Prosthetic valve	Negative	Not done	Possible; 1 major, 2 minor	Confirmed
2	M, 83 y	Asthenia and fever	*Enterococcus faecalis*	Aortic prosthetic valve	7 y, late	Prosthetic valve	Negative	Negative	Possible; 1 major, 1 minor	Confirmed
3	M, 77 y	Fever	*Enterococcus faecalis*	Aortic prosthetic valve	7 mo, early	Prosthetic valve	Negative	Not done	Possible; 1 major, 1 minor	Confirmed
4	M, 78 y	Asthenia and fever	*Enterococcus faecalis*	Aortic prosthetic valve	6 y, late	Prosthetic valve	Negative	Not done	Possible; 1 major, 2 minor	Confirmed
5	F, 61 y	Fever and malaise	*Pseudomonas aeruginosa*	Aortic prosthetic valve, Bentall	6 mo, early	Prosthetic valve	Negative	Negative	Possible; 1 major, 2 minor	Confirmed
6	M, 50 y	Asthenia and fever	*Enterococcus faecalis*	Aortic prosthetic valve	3 mo, early	Prosthetic valve	Negative	Negative	Possible; 1 major, 1 minor	Confirmed
7	F, 83 y	Ischaemic occipital stroke and fever	*Streptococcus mutans*	Aortic prosthetic valve	2 y, late	Prosthetic valve	Negative	Not done	Possible; 1 major, 2 minor	Confirmed
8	F, 74 y	Ischaemic occipital stroke and fever	*Staphylococcus haemolyticus*	Aortic prosthetic valve, Bentall	7 mo, early	Prosthetic valve	Negative	Negative	Definite; 1 major, 3 minor	Confirmed
9	M, 70 y	Severe sepsis	*Staphylococcus epidermidis*	Aortic prosthetic valve	3 mo, early	Prosthetic valve	Negative	Abscess	Definite; 2 major	Confirmed
10	F, 45 y	Fever and hepatitis	*Candida parapsilosis*	Aortic prosthetic valve	2 mo, early	Perivalvular abscess	Fistula	Not done	Definite; 2 major	Confirmed
11	M, 56 y	Severe sepsis	MSSA	Aortic prosthetic valve, Bentall	9 mo, early	Prosthetic valve, Bentall	Aortic vegetation	Vegetation	Definite; 2 major	Confirmed
12	M, 79 y	Fever	*Streptococcus bovis*	Biological aortic valve, Bentall	15 mo, late	Prosthetic valve, Bentall	Aortic vegetation	Not done	Definite; 2 major	Confirmed
13	F, 69 y	Dyspnoea and episodic fever	*Streptococcus mitis*	Biological mitral prosthesis	9 y, late	Prosthetic valve	Mitral vegetation	Vegetation	Definite; 2 major	Confirmed
14	F, 54 y	Severe sepsis	B/C negative	Aortic prosthetic valve, Bentall	28 y, late	Prosthetic valve	Leak prosthetic valve; aortic aneurysm	Not done	Definite; 2 major	Confirmed
15	M, 60 y	Bacteraemia, CVC infection	hVISA	Mitral prosthetic valve	10 y, late	Negative	Negative	Vegetation	Definite; 2 major	Confirmed
16	M, 72 y	Fever and lung cancer	MSSA	Aortic prosthetic valve	12 y, late	Negative	Aortic vegetation	Not done	Definite; 2 major	Confirmed
17	M, 76 y	Fever	*Staphylococcus hominis*	Aortic prosthetic valve	3 y, late	Negative	Negative	Negative	Possible; 1 major, 2 minor	Rejected
18	M, 42 y	Fever	B/C negative	Aortic prosthetic valve	16 mo, late	Negative	Negative	Not done	Possible; 5 minor	Rejected
19	M, 62	Dyspnoea and chest pain	*Enterococcus faecalis*	Aortic prosthetic valve, Bentall	13 mo, late	Prosthetic valve	Detachment of valve pseudo-aneurysm	Not done	Definite; 2 major	Confirmed
20	M, 43	Septic shock	*Pseudomonas aeruginosa*	Aortic prosthetic valve, Bentall	10 mo, early	Prosthetic valve	Negative	Not done	Possible; 1 major, 2 minor	Confirmed
21	M, 50 y	Fever	*Enterococcus faecalis*	Native aortic	NA	Negative	Aortic vegetation	Not done	Definite; 2 major	Confirmed
22	M, 63 y	Fever and pneumonia	*Staphylococcus haemolyticus*	Native aortic	NA	Negative	Aortic vegetation	Not done	Definite; 2 major	Confirmed
23	M, 67 y	Fever	*Streptococcus oralis*	Native mitral	NA	Negative	Flail posterior leaflet	Flail posterior leaflet	Definite; 2 major	Confirmed
24	F, 59 y	Ischaemic occipital stroke and fever	B/C negative	Native aortic/mitral	NA	Negative	Aortic and mitral vegetations	Not done	Possible; 1 major, 2 minor	Confirmed
25	M, 41 y	Aortic vegetation, fever and malaise	B/C negative, *Enterococcus spp*[a]	Native aortic	NA	Negative	Aortic vegetation	Vegetation	Possible; 1 major, 1 minor	Confirmed
26	M, 51 y	Fever (1 month)	B/C negative	Native aortic	NA	Negative	Aortic vegetation	Not done	Possible; 1 major, 1 minor	Confirmed
27	M, 72 y	Fever (1 month)	*Streptococcus parasanguinis*	Native aortic	NA	Negative	Mitral vegetation	Not done	Definite; 2 major	Confirmed

TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; IE, infective endocarditis; M, male; F, female; mo, months; y, years; MSSA, methicillin-sensitive *Staphylococcus aureus*; B/C, blood culture; CVC, central venous catheter; hVISA, heterogeneous vancomycin-intermediate *Staphylococcus aureus*.

[a] Organism identified through molecular testing.

Table 2
Comparison of the revised Duke criteria evaluation, TTE or TEE echo findings, and ^{18}F-FDG-PET–CT scan results of 22 out of the 27 patients with suspected IE

		IE confirmed	IE not confirmed	
A. Results of the total population of 22 patients		(*n* = 20)	(*n* = 2)	
Duke criteria	Definite	14	0	Sensitivity 70%; specificity 100%; PPV 100%; NPV 25%
	Possible	6	2	
Echocardiography[a]	Positive	16	0	Sensitivity 80%; specificity 100%; PPV 100%; NPV 33%
	Negative	4	2	
^{18}F-FDG-PET–CT	Positive	11	0	Sensitivity 55%; specificity 100%; PPV 100%; NPV 18%
	Negative	9	2	
B. Results of 15 patients with suspected PVE		(*n* = 13)	(*n* = 2)	
Duke criteria	Definite	10	0	Sensitivity 77%; specificity 100%; PPV 100%; NPV 40%
	Possible	3	2	
Echocardiography[a]	Positive	9	0	Sensitivity 69%; specificity 100%; PPV 100%; NPV 33%
	Negative	4	2	
^{18}F-FDG-PET–CT	Positive	11	0	Sensitivity 85%; specificity 100%; PPV 100%; NPV 50%
	Negative	2	2	
C. Results of 7 patients with suspected NVE		(*n* = 7)	(*n* = 0)	
Duke criteria	Definite	4	0	Sensitivity 57%; specificity NE; PPV 100%; NPV NE
	Possible	3	0	
Echocardiography[a]	Positive	7	0	Sensitivity 100%; specificity NE; PPV 100%; NPV NE
	Negative	0	0	
^{18}F-FDG-PET–CT	Positive	0	0	Sensitivity NE; specificity NE; PPV NE; NPV NE
	Negative	7	0	

IE, infective endocarditis; TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; ^{18}F-FDG-PET–CT, combined fluorodeoxyglucose labelled with fluorine-18 positron emission tomography and computed tomography; PPV, positive predictive value; NPV, negative predictive value; PVE, prosthetic valve endocarditis; NVE, native valve endocarditis; NE, not evaluable.
[a] Positive: patients with a positive TEE or TTE; negative: patients with a negative TEE and TTE.

to rule out infection (NPV) was low for all of the diagnostic tools used (18–33%), and ^{18}F-FDG-PET–CT did not provide any additional diagnostic value to the revised Duke criteria. However, when patients with PVE and NVE were analysed separately, several interesting results emerged. ^{18}F-FDG-PET–CT was the most effective tool at diagnosing PVE, with a sensitivity of 85% and an NPV of 50% when evaluated against the results obtained by echocardiography. In addition, 89% overall of confirmed PVE had a positive ^{18}F-FDG-PET–CT result. The revised Duke criteria and echocardiography findings showed good, although reduced compared to ^{18}F-FDG-PET–CT, sensitivity for PVE (77% and 69%, respectively), but a poor ability to rule out the diagnosis (NPV 28% and 25%, respectively). The situation was completely reversed in patients with NVE: ^{18}F-FDG-PET–CT failed to detect the infection in all cases, demonstrating that this tool is not appropriate for establishing or ruling out infection of native cardiac valves.

Recent guidelines have highlighted how echocardiography findings and microbiology results can be inconclusive in patients with cardiac devices or valvular prostheses.[2,3] This is often related to the elusive clinical presentation and the challenging interpretation of the echocardiography findings (thickened valves, nodules, or valvular calcifications) in the presence of prosthetic devices. Recent studies have investigated the role of ^{18}F-FDG-PET–CT in detecting infectious foci in critically ill patients and in detecting IE complications, and some clinical reports have suggested the feasibility and potential value of the ^{18}F-FDG-PET–CT scan in diagnosing IE.[18,19] A number of individual case reports and a small clinical series have reported conflicting results regarding the use of ^{18}F-FDG-PET–CT as an additional diagnostic tool in situations where other tests have failed to provide a definitive diagnosis. Yen et al.[20] demonstrated that ^{18}F-FDG-PET–CT could diagnose IE that was confirmed by positive blood cultures in a study of six patients, and Mogadam-Kia et al.[21] demonstrated increased ^{18}F-FDG-PET–CT uptake in the prosthetic valve that was consistent with IE in a patient with prolonged fever and an absence of clear vegetations. Conversely, Kouijzer et al. recently reported an ^{18}F-FDG-PET–CT sensitivity of 39% (specificity 93%) in a population of 18 patients with IE,[22] demonstrating the low diagnostic power of this tool. In this study, only two patients had PVE, and one of these patients had positive ^{18}F-FDG-PET–CT findings. In a recent paper by Saby et al. regarding PVE, ^{18}F-FDG-PET–CT demonstrated a PPV of 85%, and the authors proposed the addition of abnormal FDG uptake around the prosthetic valve as a new major criterion of the modified Duke criteria.[23] Millar and colleagues[24] recently reviewed more than 30 published papers on the potential role of ^{18}F-FDG-PET–CT in the diagnosis of IE. The authors highlighted the limitations of echocardiography in the presence of a cardiac prosthetic valve infection and the potential advantages of ^{18}F-FDG-PET–CT, of which the reported overall sensitivity on PVE was 83.3% vs. 27.2% for echocardiography. Similar results were reported by Sarrazin and co-workers regarding cardiovascular implantable electronic device infections, in which ^{18}F-FDG-PET–CT was positive in 76% (32/42) of the infected device cases compared to the lack of uptake in six control patients.[25] In a more recent paper, Erba et al. summarized the published evidence regarding the usefulness of ^{18}F-FDG-PET–CT in the diagnosis of IE. The authors support the use of ^{18}F-FDG-PET–CT, in association with echocardiography, to confirm or rule out IE in equivocal or difficult to explore situations, such as those due to artefacts caused by mechanical prostheses or device catheters.[26]

As with other imaging options, ^{18}F-FDG-PET–CT does not identify infection per se. Rather it identifies the metabolically active cells, such as leukocytes, that are responding to inflammation or infection. Similarly, suppression of infection by a prolonged course of antibiotics prior to ^{18}F-FDG-PET–CT scanning may result in false-negative images. Moreover, some authors have suggested that limited uptake of the ^{18}F-FDG tracer can be due to small vegetation sizes below the detection threshold of the tracer.[27] Additionally, hyperglycaemia may interfere with this process and can lead to false-negative results. In our study, these reasons do not explain the negative ^{18}F-FDG-PET–CT scans in patients with NVE. More likely, as some authors have suggested, the ^{18}F-FDG-PET–CT scans do not show vegetations that are normally seen by TTE/TEE; rather, ^{18}F-FDG-PET–CT shows valvular and perivalvular infections indicative of infectious processes or small abscesses at the valvular position, which are more easily detectable in the case of prosthetic

infections.[18] False-positive scans may also occur in patients with recently implanted vascular devices.[19] In our study, eight patients had early PVE, which occurred less than 12 months after surgery (mean 5 months, range 3–9 months). All of these patients had confirmed IE on the basis of positive blood cultures for a typical microorganism and positive ^{18}F-FDG-PET–CT results at the site of engraftment, without any other possible sources of infection.

Several studies have evaluated the role of ^{18}F-FDG-PET–CT in the diagnosis of focal infections or inflammatory diseases in critically and non-critically ill patients, and have found a NPV of nearly 100%, thus concluding that negative ^{18}F-FDG-PET–CT scans almost certainly appear to exclude focal infections as a cause of clinical symptoms.[12] Moreover, a recent extensive study described the excellent sensitivity and anatomical precision of ^{18}F-FDG-PET–CT for the early detection of embolisms and metastatic infections secondary to IE.[18] In our study population, ^{18}F-FDG-PET–CT also demonstrated peripheral embolism (cerebral, splenic, and intestinal) in six cases (five PVE and one NVE) (data not shown).

Before drawing conclusions, some limitations of our study must be discussed. First, the small number of patients studied does not provide sufficient strength for the routine use of ^{18}F-FDG-PET–CT for PVE diagnosis. Second, we evaluated cases of IE admitted consecutively to our infectious diseases ward, coming from other wards of the hospital in which the suspected diagnosis was based on the modified Duke criteria. This could be considered a bias of our study, as we enrolled consecutive patients with a strong suspicion of IE and this explains the very low number of patients for whom the IE diagnosis was rejected.

Otherwise, taking into account the limitations mentioned above, the results of the present study suggest the potential advantage of ^{18}F-FDG-PET–CT in the diagnosis of IE in patients with prosthetic cardiac valves, particularly in cases in whom negative echocardiography findings or negative blood cultures make a defined IE diagnosis difficult.

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