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CLINICAL RESEARCH

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography for the diagnosis of native valve infective endocarditis: A prospective study☆

La tomographie par émission de positons au ^{18}F-fluorodeoxyglucose couplée a la tomodensitométrie pour le diagnostic d'endocardite infectieuse sur valve native : une étude prospective

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Abbreviations: CT, computed tomography; DSU, diffuse splenic uptake; ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

☆ Despite limited sensitivity, ^{18}F-FDG PET/CT is useful in native valve infective endocarditis, because of its excellent specificity and its ability to detect metastatic embolism.

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KEYWORDS
Valve disease;
Endocarditis;
Guidelines;
Nuclear imaging

Summary
Background. — ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has recently been added as a major criterion in the European Society of Cardiology (ESC) 2015 infective endocarditis guidelines. PET/CT is currently used in patients with suspected prosthetic valve and cardiac device-related endocarditis. However, the value of the ESC classification and the clinical impact of PET findings are unknown in patients with native valve endocarditis (NVE).
Aims. — Our aims were: to assess the value of the ESC criteria (including PET/CT) in NVE; to determine the usefulness of PET/CT concerning embolic detection; and to describe a new PET/CT feature (diffuse splenic uptake).
Methods. — Between 2012 and 2017, 75 patients with suspected NVE were included prospectively, after exclusion of patients with uninterpretable or unfeasible PET/CT. Using gold standard expert consensus, 63 cases of infective endocarditis were confirmed and 12 were rejected.
Results. — Significant valvular uptake was observed in 11 of 63 patients with definite NVE and in no patients who had the diagnosis of infective endocarditis rejected (sensitivity 17.5%, specificity 100%). Among the 63 patients with NVE, a peripheral embolism or mycotic aneurysm was observed in 20 (31.7%) cases. Application of the ESC criteria increased Duke criteria sensitivity from 63.5% to 69.8% ($P < 0.001$), without a change in specificity. Diffuse splenic uptake was observed in 39 (52.0%) patients, including 37 (58.7%) with a final diagnosis of NVE (specificity 83.3%).
Conclusions. — ^{18}F-FDG PET/CT has poor sensitivity but high specificity in the diagnosis of NVE. The usefulness of ^{18}F-FDG PET/CT is high for embolic detection. Diffuse splenic uptake represents a possible new diagnostic criterion for NVE.

MOTS CLÉS
Valvulopathie ;
Endocardite ;
Recommandations ;
Imagerie nucléaire

Résumé
Contexte. — La tomographie par émission de positons au ^{18}F-fluorodéoxyglucose couplée au scanner (TEP/TDM au ^{18}F-FDG) a récemment été ajoutée comme critère diagnostique majeur dans les recommandations de l'ESC 2015 sur la prise en charge de l'endocardite infectieuse (EI). Notre équipe, ainsi que d'autres, ont montré l'utilité de la TEP/TDM chez les patients suspects d'EI sur valve prothétique ou matériel intracardiaque. Cependant, la sensibilité et la spécificité de la classification ESC restent inconnues dans les EI sur valves natives, tout comme l'impact clinique des données TEP.
Objectifs. — Objectif primaire: évaluer la valeur des nouveaux critères diagnostiques ESC incluant les données TEP/TDM dans les EI sur valves natives. Objectifs secondaires: déterminer l'utilité de la TEP/TDM au ^{18}F-FDG concernant la détection d'emboles ou de lésions néoplasiques; décrire un nouveau critère en TEP; la fixation splénique diffuse.
Méthodes. — Entre 2012 et 2017, 75 patients suspects d'EI sur valves natives ont été inclus de façon prospective, après exclusion des patients pour lesquels la TEP/TDM était ininterprétable ou non réalisable. Après avis du consensus d'experts (« Endocarditis Team »), 63 EI ont été confirmées et 12 ont été éliminées. Le suivi des patients a été programmé à 1, puis 3 mois après la sortie d'hospitalisation.
Résultats. — Une fixation valvulaire significative en TEP/TDM au ^{18}F-FDG (critère majeur) a été observée chez 11 patients sur 63 EI certaines, versus aucune dans le groupe témoin (sensitivité 17,5 %, spécificité 100 %). Un embole périphérique ou une fixation vasculaire a été observé chez 20 des 63 EI certaines (31,7 %). L'implémentation des données TEP dans les critères diagnostiques a permis une amélioration de la sensibilité de 63,5 % à 69,8 % ($p < 0,001$) sans modification de spécificité. Une fixation splénique diffuse a été mise en évidence chez 39 (52,0 %) patients, dont 37 (58,7 %) classés EI certaines (spécificité 83,3 %).
Conclusions. — La valeur diagnostique de la fixation valvulaire en TEP/TDM au ^{18}F-FDG est faible dans les EI sur valves natives (sensibilité 17,5 %), mais est utile pour la détection d'emboles septiques ou de lésions secondaires. L'application des critères ESC 2015 incluant le TEP/TDM augmente modérément la sensibilité des critères de Duke, sans en réduire la spécificité. Notre étude décrit pour la première fois l'apport de la fixation splénique diffuse, correspondant à un potentiel nouveau critère diagnostique d'endocardite infectieuse sur valve native.

Background

Diagnosis of infective endocarditis (IE) is challenging. Although several diagnostic criteria have been proposed [1—4], the decision to initiate antibiotic therapy is frequently based on an expert consensus. The value of Duke criteria is less than perfect, and has been shown to be lower in some subgroups (prosthetic valves, cardiac devices, transaortic valve replacement), particularly because of the lower sensitivity of echocardiography in these patients [5—9]. We [10,11] and others [12—21] have demonstrated that ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is useful in patients with suspected prosthetic valve endocarditis (PVE) or cardiac device-related endocarditis. For this reason, a positive uptake by PET/CT has been included in the new ESC criteria [3], as both a major criterion (prosthetic valve uptake) and a minor criterion (embolic event) [11,16,22—25]).

However, data concerning patients with native valve endocarditis (NVE) are scarce [18,26,27], with low sensitivity reported in some relatively small recent studies with PET/CT [28,29].

The aim of our study was to prospectively assess the value of the new ESC criteria, including PET/CT findings, in the diagnosis of NVE.

Methods

From February 2012 to March 2017, 75 patients with suspected NVE underwent PET/CT. Using the expert consensus of the Endocarditis team after a 3-month follow-up as gold standard, 63 cases of IE were confirmed and 12 were rejected. Exclusion criteria were pregnancy, inability to lie flat, need for urgent cardiac surgery, haemodynamic instability and high blood glucose concentration, intracardiac device, failure of ketogenic diet, myocardial uptake and antibiotic therapy initiated more than 2 weeks ago.

The primary endpoint of this study was the number of major (valvular uptake) and minor (peripheral uptake) PET/CT criteria observed in patients with and without NVE.

The secondary endpoint was the change in diagnostic criteria sensitivity and specificity associated with the addition of PET/CT results.

Clinical, microbiological and echocardiographic data

Clinical data included age, sex, height, weight, blood pressure and personal history (IE, intravenous drug use, high blood pressure, atrial fibrillation, myocardial infarction, stroke, peripheral arterial disease, chronic renal failure, respiratory insufficiency, dialysis, cancer, heart failure, peripheral embolisms, atrioventricular conduction defect, periannular complications and indication for cardiac surgery). Transthoracic and transoesophageal echocardiography were performed in all patients, and were considered positive in the presence of vegetation or periannular extension (abscess, pseudoaneurysm, fistula, perforation) [6]. Laboratory studies included leukocyte count, platelets, serum C-reactive protein concentration, liver function, kidney function, brain natriuretic peptide concentration and complete blood count. Microbiological data included blood culture, serology testing, valve culture and polymerase chain reaction from a valve specimen (according to international guidelines).

^{18}F-FDG PET/CT

Patients fasted for 12 hours before ^{18}F-FDG PET/CT to limit physiological myocardial 18-FDG uptake. Patients received a low-carbohydrate high-fat high-protein meal before ^{18}F-FDG PET/CT (General Electric, Milwaukee, WI, USA). Imaging started 60 minutes after 18-FDG injection (5 MBq/kg) with a non-enhanced low-dose computer tomography (CT) scan (120 kV, 80 mA) with body PET acquisition in 3-dimensional mode. PET/CT acquisition evolved during the study: imaging was performed to the root of the thighs from 2014 to 2016, to the knees from 2016 to 2017 (in order to diagnose mycotic aneurysms) and then to the feet. Transverse PET slices were reconstructed into a 256×256 matrix using the OSEM (ordered-subset-expectation-maximisation) algorithm. The PET data were linked with the CT data. The data analysis (Xeleris; General Electric, Milwaukee, WI, USA) was based on visual interpretation. Assessment of ^{18}F-FDG uptake was performed by two experienced and blinded nuclear medicine physicians. For the visual analysis, hypermetabolic intensities in the valvular area were considered abnormal, and pathological uptake had to be confirmed in the uncorrected images. Patients with myocardial uptake were considered as uninterpretable, in order to obtain clear results on valvular uptake. The data analysis was based on visual interpretation only. Visual analysis identified positive PET as a presence of hypermetabolic intensities in the valvular area. Only visual data were used, in a binary way (positive or negative). A semiquantification was added, based on the uptake intensity degree related to the basal liver uptake: low, medium or high intensity. In addition, other pathological uptakes were reported, including peripheral uptake suggestive of septic embolism (splenic, renal), an uptake possibly revealing an infectious source (e.g. dental or colic), as well as indirect uptake, such as osteomedullary or splenic diffuse enhancement (positive if exceeding liver uptake).

Gold standard

The final diagnosis was defined by an expert team, according to the clinical and/or pathological modified Duke criteria, and determined from the data collected during a 3-month follow-up after admission.

Statistical analysis

All statistical analyses were carried out with the software programme R, version 3.4.1. All of the tests were two sided. A P value < 0.05 was considered to be significant.

A descriptive analysis of the entire study population was first performed. Qualitative variables are expressed as numbers and percentages, and were compared using the χ^2 test (or Fisher's test, as appropriate). Quantitative variables are expressed as means, and were compared using Student's test (or the Mann—Whitney test, as appropriate).

Table 1 Baseline characteristics of the 75 patients with suspected native valve endocarditis.

	All ($n = 75$)	Definite NVE ($n = 63$)	Rejected NVE ($n = 12$)	*P*
Endocarditis location				
Aortic	25 (33.3)	25 (39.7)	0 (0.0)	1.00
Mitral	38 (50.7)	38 (60.3)	0 (0.0)	1.00
Demographic and clinical data				
Age (years)	65 (21—88)	64 (21—88)	68 (48—84)	0.20
Male sex	52 (69.3)	47 (74.6)	5 (41.7)	0.038
Active smoking	21 (28.0)	18 (28.6)	3 (25.0)	1.00
Diabetes mellitus	10 (13.3)	7 (11.1)	3 (25.0)	0.20
History of atrial fibrillation	11 (14.7)	8 (12.7)	3 (25.0)	0.37
History of stroke	4 (5.3)	3 (4.8)	1 (8.3)	0.51
History of IE	5 (6.7)	5 (8.0)	0 (0.0)	0.59
HIV	2 (2.7)	2 (3.2)	0 (0.0)	1.00
Drug addiction	5 (6.7)	4 (6.3)	1 (8.3)	1.00
Dialysis	1 (1.3)	1 (1.6)	0 (0.0)	1.00
Respiratory insufficiency	4 (5.3)	3 (4.8)	1 (8.3)	0.51
Cancer	15 (20.0)	14 (22.2)	1 (8.3)	0.44
Heart failure	18 (24.3)	16 (25.8)	2 (16.7)	0.72
Septic shock	2 (2.7)	1 (1.6)	1 (8.3)	0.30
Biological data				
Creatinine (μmol/L)	105 (44—898)	109 (44—898)	87 (46—140)	0.21
Leukocyte count (G/L)	9.9 (2.7—24.0)	10.3 (4.4—24.0)	8.0 (2.7—12.0)	0.028
CRP (mg/L)	91.4 (1.3—378.0)	98.3 (1.3—378.0)	55.6 (14.0—179.0)	0.046
Platelets (G/L)	280 (54—637)	265 (54—510)	358 (140—637)	0.06
BNP (ng/L)	351 (9—3352)	369 (9—3352)	209 (29—905)	0.21
Microbiological data				
Positive blood cultures	53 (70.7)	48 (76.2)	5 (41.7)	0.033
Enterococcus species	8 (10.7)	8 (12.7)	0 (0)	> 0.005
Staphylococcus aureus	16 (21.3)	12 (19.0)	4 (33.3)	> 0.005
Coagulase-negative *Staphylococcus*	3 (4.0)	3 (4.8)	0 (0.0)	> 0.005
Oral *Streptococcus*	10 (13.3)	10 (15.9)	0 (0.0)	> 0.005
Streptococcus gallolyticus	6 (8.0)	6 (9.5)	0 (0.0)	> 0.005
Gram-negative bacteria	3 (4.0)	3 (4.8)	0 (0.0)	> 0.005
Other bacteria	12 (16.7)	12 (19.4)	0 (0.0)	> 0.005
Echocardiographic data				
LVEF (%)	64 (43—75)	65 (43—75)	62 (50—70)	0.13
Positive echocardiography	46 (61.3)	46 (73.0)	0 (0.0)	< 0.001
Vegetation	46 (61.3)	46 (73.0)	0 (0.0)	< 0.001
Abscess	4 (5.3)	4 (6.3)	0 (0.0)	1
Severe valvular regurgitation	42 (56.0)	42 (65.6)	0 (0.0)	< 0.001
Surgery	33 (44.0)	33 (52.4)	0 (0.0)	< 0.001
Embolism (clinical/CT/MRI)	28 (37.8)	28 (45.2)	0 (0.0)	< 0.001

Data are expressed as number (%) or mean (range). BNP: brain natriuretic peptide; CRP: C-reactive protein; CT: computed tomography; HIV: human immunodeficiency virus; IE: infective endocarditis; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NVE: native valve endocarditis.

In order to evaluate the ability of PET to identify patients diagnosed with endocarditis among patients classified as having ''possible'' endocarditis (using the Duke criteria), a paired percentages comparison test was performed (McNemar's test with correction of continuity, in view of the small population). The interobserver variability of PET/CT (using the standardised form) was assessed using the kappa test.

Results

Baseline characteristics

One hundred and sixty-two patients were included initially; among them, 51 were excluded, mainly because the time from initiation of antibiotic therapy exceeded 14 days. A further 36 patients were omitted because of high glucose

Table 2 Detailed results of positron emission tomography/computed tomography.

	All ($n = 75$)	Definite NVE ($n = 63$)	Rejected NVE ($n = 12$)	*P*
Delay from antibiotic therapy initiation (days)	8.7 (0—60)	9.3 (0—60)	5.6 (0—14)	0.06
Valvular uptake	11 (14.7)	11 (17.5)	0 (0.0)	0.19
Myocardial uptake	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Aortic uptake	3 (4.0)	3 (4.8)	0 (0.0)	1.00
Mitral uptake	9 (12.0)	9 (14.3)	0 (0.0)	0.34
Tricuspid uptake	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Peripheral emboli	21 (28.0)	20 (31.7)	1 (8.3)	0.16
Spondylodiscitis	15 (20.0)	15 (23.8)	0 (0.0)	0.11
Diffuse splenic uptake	39 (52.0)	37 (58.7)	2 (16.7)	0.011

NVE: native valve endocarditis.

concentration or ketogenic diet failure with myocardial uptake. Finally, 75 patients (mean age 65 years, range 21—88 years; 69.3% men) were included during the study period, of whom 63 had a final diagnosis of IE. The baseline characteristics are summarised in Table 1. The major reason for exclusion was the presence of myocardial uptake (even minimal) as a result of ketogenic diet not being respected ($n = 36$).

Diagnostic value of PET/CT

Major criterion: Valvular uptake

PET/CT was performed at a median of 8.7 days after antibiotic initiation (Table 2). Among the 63 patients with a final diagnosis of NVE, echocardiography was positive in 46 patients (73.0%) and PET valvular uptake was observed in 11 (17.5%) cases (Fig. 1). Among the 12 patients without NVE, no patient had positive echocardiography or PET/CT concerning the valve uptake (no false positive cases). No influence of potential confounding factors between positive and negative PET/CTs was identified (Table 3). Notably, vegetation size and time between initiation of antibiotic therapy and PET/CT did not affect the PET/CT result (Table 3).

Minor criteria: Peripheral embolism or mycotic aneurysm detected by PET/CT

Among the 63 patients with a final diagnosis of NVE, a peripheral embolism or vascular uptake (suggesting a mycotic

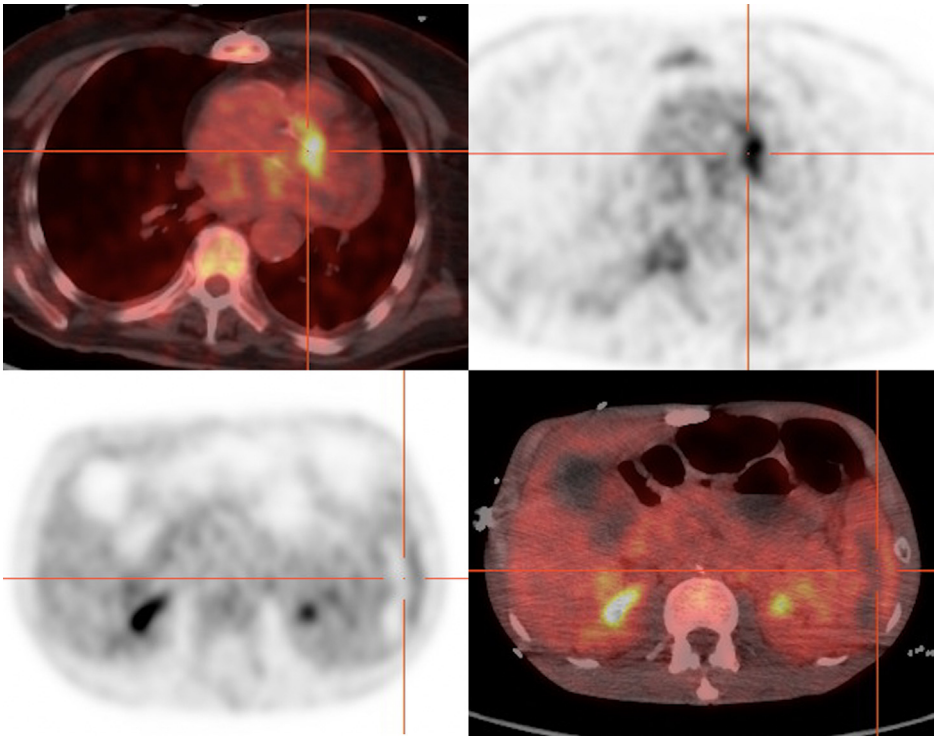

Figure 1. Native valvular uptake and splenic emboli on positron emission tomography/computed tomography (PET/CT) in a 75-year-old patient presenting with *Staphylococcus aureus* mitral endocarditis (12 mm vegetation on transoesophageal echocardiography). This examination is fully contributing to native valve endocarditis (NVE) diagnosis in this patient (one major criterion and one minor criterion classifying the patient as having definite NVE).

Table 3 Positive versus negative positron emission tomography/computed tomography in 63 definite cases of native valve endocarditis.

	Definite NVE ($n=63$)	PET+ ($n=11$)	PET− ($n=52$)	*P*
Demographic and clinical data				
Age (years)	64 (21–88)	66 (36–82)	63 (21–88)	0.63
Male sex	47 (74.6)	6 (54.5)	41 (78.8)	0.13
Active smoking	18 (28.6)	5 (45.5)	13 (25.0)	0.13
Diabetes mellitus	7 (11.1)	0 (0.0)	7 (13.5)	0.34
History of atrial fibrillation	8 (12.7)	2 (18.2)	6 (11.5)	0.62
History of stroke	3 (4.8)	0 (0.0)	3 (5.8)	1.00
History of IE	5 (8.0)	1 (9.1)	4 (7.7)	1.00
HIV	2 (3.2)	0 (0.0)	2 (3.8)	1.00
Drug addiction	4 (6.3)	0 (0.0)	4 (7.7)	1.00
Dialysis	1 (1.6)	1 (9.1)	0 (0.0)	0.18
Respiratory insufficiency	3 (4.8)	0 (0.0)	3 (5.8)	1.00
Cancer	14 (22.2)	3 (27.3)	11 (21.2)	0.70
Heart failure	16 (25.8)	3 (27.3)	13 (25.0)	1.00
Septic shock	1 (1.6)	0 (0.0)	1 (1.9)	1.00
Delay between antibiotic therapy and PET/CT (days)	8.3 (0–14)	8.7 (4–14)	8.3 (0–14)	0.68
Biological data				
Creatinine (μmol/L)	109 (44–898)	157 (44–898)	99 (46–262)	0.46
Leukocyte count (G/L)	10.3 (4.4–24.0)	11.2 (4.4–24.0)	10.1 (4.4–22.0)	0.61
CRP (mg/L)	98.3 (1.3–378.0)	157.0 (9.0–350.0)	85.7 (1.3–378.0)	0.14
Platelets (G/L)	265 (54–510)	231 (145–329)	273 (54–510)	0.09
BNP (ng/L)	369 (9–3352)	387 (17–1214)	365 (9–3352)	0.88
Microbiological data				
Positive blood cultures	48 (76.2)	8 (72.7)	39 (76.5)	1.00
Enterococcus species	8 (12.7)	0 (0.0)	8 (15.7)	> 0.005
Staphylococcus aureus	12 (19.0)	4 (36.4)	8 (15.7)	> 0.005
Coagulase-negative *Staphylococcus*	3 (4.8)	0 (0.0)	3 (5.8)	> 0.005
Oral *Streptococcus*	10 (15.9)	1 (9.1)	9 (17.3)	> 0.005
Streptococcus gallolyticus	6 (9.5)	2 (18.2)	4 (7.7)	> 0.005
Gram-negative bacteria	3 (4.8)	0 (0.0)	3 (5.8)	> 0.005
Other bacteria	12 (19.4)	1 (9.1)	11 (21.2)	> 0.005
Echocardiographic data				
LVEF (%)	65 (43–75)	66 (60–75)	65 (43–70)	0.46
Positive echocardiography	46 (73.0)	10 (90.9)	36 (69.2)	0.26
Vegetation	46 (73.0)	11 (100.0)	35 (67.3)	0.027
Vegetation size (mm)	9 (0–50)	12 (5–24)	9 (0–50)	0.16
Abscess	4 (6.3)	2 (18.2)	2 (3.8)	0.14
Severe valvular regurgitation	42 (65.6)	3 (27.3)	39 (76.5)	0.004
Surgery	33 (52.4)	6 (54.5)	27 (51.9)	1.00
Embolism (clinical/CT/MRI)	28 (45.2)	6 (54.5)	22 (42.3)	0.52

Data are expressed as number (%) or mean (range). BNP: brain natriuretic peptide; CRP: C-reactive protein; CT: computed tomography; HIV: human immunodeficiency virus; IE: infective endocarditis; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NVE: native valve endocarditis; PET: positron emission tomography.

aneurysm) was observed in 20 (31.7%) cases: eight splenic emboli (13%) and 12 pulmonary uptakes suggesting embolism (19%). One vascular uptake was found in a patient classified as having the diagnosis of IE rejected (Table 2).

Duke versus ESC criteria

Among the 63 patients with a final diagnosis of IE, 40 were correctly classified as having definite IE by Duke criteria (sensitivity 63.5%), 13 (20.6%) were classified as having possible IE and 10 had the diagnosis of IE rejected (15.9%) (Table 4 and Fig. 2). Addition of PET/CT major or minor ESC criteria allowed the correct identification of four additional patients, switching from possible to definite IE as a result of a new major PET criterion in three and a new minor PET criterion in two (one patient had both major and minor PET criteria). The sensitivity of the ESC criteria was 69.8%. Among the 12 cases that had the diagnosis of IE rejected, none was classified as having definite IE by the ESC classification (specificity 100%).

Table 4 Additional value[a] of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography over Duke criteria.

	Final diagnosis	
	Definite NVE ($n = 63$)	Rejected NVE ($n = 12$)
Duke criteria		
Definite NVE	40 (63.5)	0 (0.0)
Possible or rejected NVE	23 (36.5)	12 (100.0)
ESC 2015 criteria		
Definite NVE	44 (69.8)	0 (0.0)
Possible or rejected NVE	19 (30.2)	12 (100.0)

Data are expressed as number (%). ESC: European Society of Cardiology; NVE: native valve endocarditis.
[a] Implementation of positron emission tomography valvular uptake: sensitivity of the classification increased from 63.5% to 69.8% ($P < 0.001$) without change in specificity.

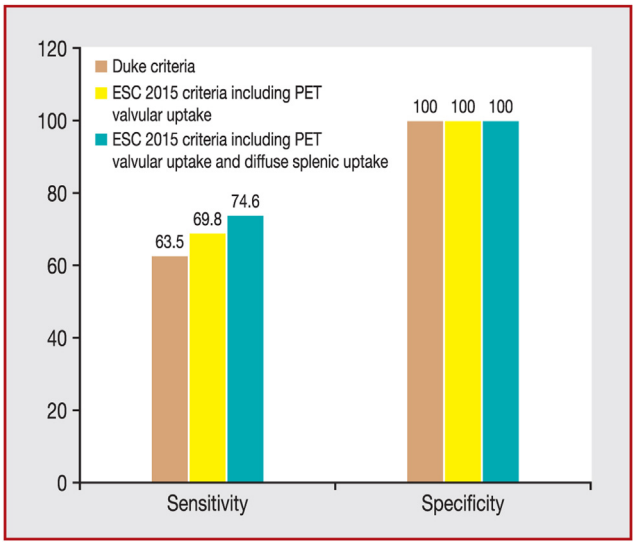

Figure 2. Additional value of positron emission tomography (PET) valvular uptake and diffuse splenic uptake in infective endocarditis diagnosis classification. ESC: European Society of Cardiology.

Diffuse splenic uptake

Diffuse splenic uptake (DSU) was observed in 39 (52.0%) patients, including 37 (58.7%) with a final diagnosis of NVE, and only two (16.7%) who had the diagnosis of NVE finally rejected ($P = 0.011$) (Fig. 3). Implementing DSU as a minor criterion over ESC criteria increased the sensitivity to 74.6% ($P < 0.001$) by reclassifying three possible cases of IE as definite IE (Fig. 4), without a significant change in specificity. Potential suspected confounders (C-reactive protein, leucocytosis, diabetes and history of cancer) were tested, and did not influence the presence of DSU (Table A.1).

Other PET findings: Secondary infectious sites or infectious portal of entry

Among the 63 patients with a final diagnosis of NVE, we found peripheral uptakes unrelated to emboli or vascular aneurysm. Fifteen (23.8%) patients were diagnosed with spondylodiscitis, not found on other imaging techniques (CT, magnetic resonance imaging), and this finding justified prolongation of the duration of antibiotic therapy. In five (7.9%) patients, colic uptake was detected, without digestive pathogens in blood cultures, indicating colonoscopy. Thyroidal uptake was observed in one (1.6%) patient, allowing the detection of an unknown malignant tumour. In three (4.8%) patients, a dental infectious site was detected by PET/CT.

Among the 12 patients with no IE diagnosis, PET/CT helped to find the infectious site in three patients (Table A.2). Finally, PET/CT was completely negative in only four patients.

Discussion

The main results of our study are as follows:

- ^{18}F-FDG PET/CT in NVE diagnosis lacks sensitivity (17.5%), reaffirming literature data in a large cohort, but presents with very high specificity (100%);
- the usefulness of PET/CT is high for diagnosing embolic events or secondary lesions;
- the presence of DSU uptake on ^{18}F-FDG PET/CT is a potential new criterion for NVE.

Value of ^{18}F-FDG PET/CT for the diagnosis of NVE

The low sensitivity of PET/CT in NVE diagnosis in our series (17.5%) is consistent with the small amount of data published previously on this topic. In 2004, Yen et al. [27] described a positive uptake in a small number of NVE cases ($n = 4$). Later studies found a lower sensitivity (39% in 18 patients in a study by Kouijzer et al. in 2013 [26], and no positive cases in seven patients in a study by Ricciardi et al. in 2014 [18]). The conclusion of these works was that PET/CT does not have a place in the positive diagnosis of NVE, at least concerning valvular uptake. Similar results were observed by Kouijzer et al. in 2018 [29] and de Camargo et al. in 2019 [28]. Our study, conducted on a larger number of patients (63 patients finally diagnosed with definite NVE), found that PET/CT contributed to a change in the

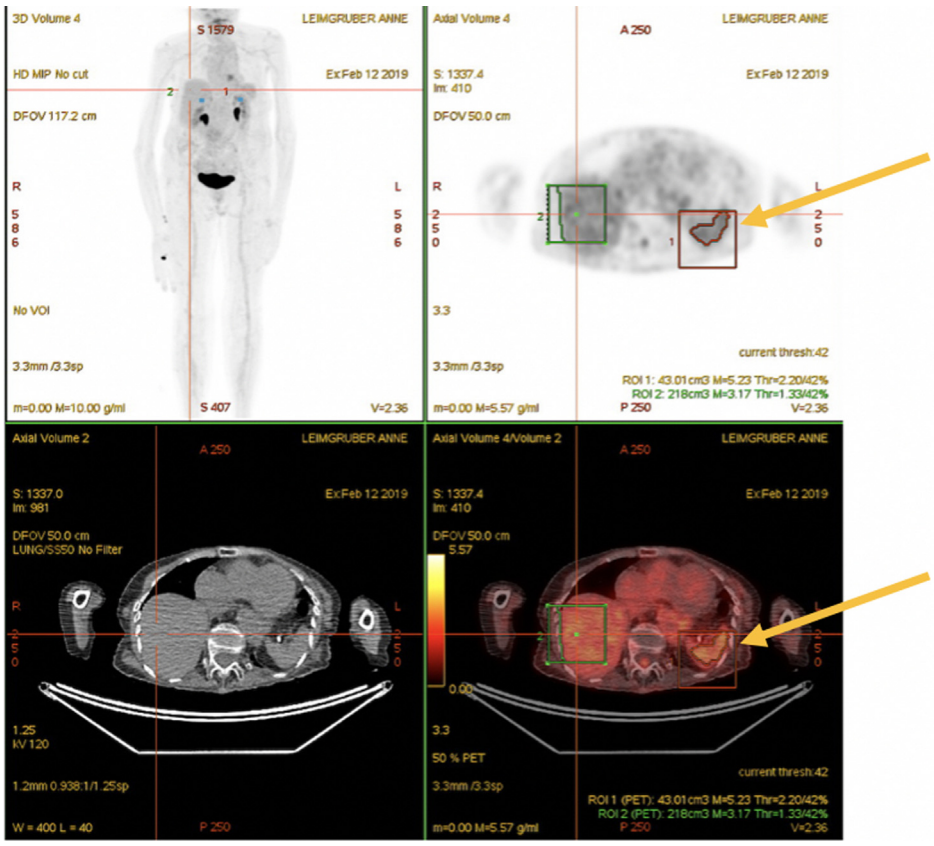

Figure 3. Diffuse splenic uptake on positron emission tomography/computed tomography. Yellow arrows show the diffuse uptake of the spleen. The red box indicates the measurement of diffuse splenic uptake, relative to the liver (green box).

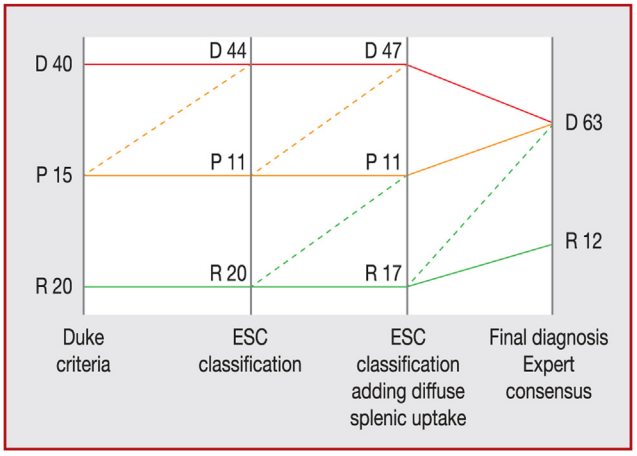

Figure 4. Reclassification of patients when adding positron emission tomography/computed tomography (PET/CT) findings. Infective endocarditis case reclassification according to the Duke criteria at admission, ESC classification and final diagnosis expert consensus at the end of the follow-up, showing the additional diagnostic input of PET/CT findings. D: definite; P: possible; R: rejected.

Duke classification from possible to definite NVE in only four patients. These results are probably related to the lack of detection of small vegetations by nuclear imaging, because of its low spatial resolution. Conversely, the specificity of valvular uptake in NVE was excellent (100% negative in the control group).

Duke versus ESC criteria in detecting embolism

Despite its low sensitivity, the addition of PET/CT uptake to the Duke criteria increased sensitivity (from 63.5% for Duke criteria to 69.8% for ESC criteria). As in PVE, the clinical effect of PET/CT seems to benefit mostly patients with ''possible'' NVE. Moreover, PET/CT was very useful for the detection of peripheral lesions (emboli, mycotic aneurysms, underlying neoplasia, etc.), as already reported [11,16,25]. In our study, 21 patients were diagnosed with emboli or mycotic aneurysm, and 21 patients with primary or secondary infectious sites. The finding of these IE complications influences disease prognosis and management, extending antibiotic therapy duration or requiring extracardiac surgery.

Global splenic uptake

DSU is a visual observation on PET/CT, corresponding to a global capture of ^{18}FDG by the organ, relative to liver uptake. This phenomenon, described and used as a potential severity criterion in oncology [24,30—32], but hardly referred to in pyogenic infections [33], has recently been reported by us [10] and others [34] as a potentially significant indirect sign of IE. We initially suspected this criterion as a tag of infectious severity, but we observed a recurrence of the DSU uptake specifically in the PET/CT of IE cases. In this prospective study, DSU was observed in 39

patients, among whom 37 had IE (resulting in a specificity of 83.3%). Despite a low sensitivity, the implementation of DSU in the ESC classification increased its sensitivity (from 69.8% to 74.6%), by reclassifying three additional possible cases of IE to definite IE. In the future, this observation could lead to the addition of DSU to the ESC diagnostic criteria, if confirmed by subsequent studies (with a larger number of patients).

Study limitations

Our results were limited by the low number of control cases and the single-centre design of the study. The choice of an expert consensus as gold standard might be criticised. However, such a gold standard has already been used in previous studies [11], and was obtained in the current study by an endocarditis team [3], including several specialists (cardiologists, infectious disease physicians, microbiologists, pathology physicians, radiologists, nuclear physicians) with extensive experience in the disease.

Another limitation of the study was the absence of quantitative analysis of PET/CT results. Semiquantitative assessment of FDG uptake, expressed as SUVmax (maximum standard uptake value) or SUVratio (standard uptake value ratio), might add additional information, but is essentially used in PVE trials [11,16,20], and was not used in our study.

Conclusions

Although its additional value is lower than in PVE, and despite limited sensitivity, ^{18}F-FDG PET/CT is useful in NVE, because of its excellent specificity and its ability to detect metastatic embolism. In addition, DSU is a possible new diagnostic criterion for NVE.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2020.10.005.

Disclosure of interest

The authors declare that they have no competing interest.

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