^{18}F-FDG-PET/CT as a diagnostic tool in native valve endocarditis

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Running head: FDG-PET/CT in native valve endocarditis

Abstract

Objective

The aim of the study is to investigate the value of ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) in diagnosing native valve endocarditis (NVE).

Methods

All patients with bacteremia and suspicion of NVE between January 2013 and June 2016 were identified from the hospitals' register and retrospectively included if echocardiography and ^{18}F-FDG-PET/CT were performed within 14 days. ^{18}F-FDG-PET/CT scans were scored independently by two nuclear medicine physicians. ^{18}F-FDG-PET/CT was compared to the modified Duke criteria and a multidisciplinary consensus.

Results

Eighty-eight patients were included. In 10 patients with definite NVE according to the modified Duke criteria, 3 patients (30.0%) had increased ^{18}F-FDG uptake in or around the heart valves and 7 patients (70.0%) had no increased ^{18}F-FDG uptake. In patients without definite NVE according to the modified Duke criteria, 89.7% (70/78) patients had no increased ^{18}F-FDG uptake in or around the heart valves. Of all 20 patients with NVE according to multidisciplinary consensus, 9 patients (45.0%) had increased ^{18}F-FDG uptake in or around the heart valves and 11 patients (55.0%) had a normal ^{18}F-FDG-PET/CT.

Conclusions

A negative ^{18}F-FDG-PET/CT result should not be interpreted as an exclusion of NVE. In patients with possible or rejected NVE according to the modified Duke criteria, ^{18}F-FDG-PET/CT could be used in case of sustained suspicion of NVE due to its high specificity in case of abnormal FDG-uptake at the valve region. ^{18}F-FDG-PET/CT is important for detecting metastatic infection which already warrants the need to perform ^{18}F-FDG-PET/CT in all patients with suspected NVE.

Key-words: ^{18}F-FDG-PET/CT; endocarditis; Duke criteria; native valve

Introduction

Infective endocarditis is a severe condition with a mortality rate up to 40% [1]. Early diagnosis of infective endocarditis is essential for successful management and improved outcome, but diagnosing endocarditis is challenging due to a variable clinical presentation with often nonspecific symptoms. For diagnosing infective endocarditis the modified Duke criteria are currently used [2]. According to these criteria, diagnosis of definite endocarditis is mainly based on positive blood cultures with typical micro-organisms and/or evidence of infective endocarditis on echocardiography. However, sensitivity of echocardiography is limited, approximately 75% for transthoracic echocardiography (TTE) and 85% - 90% for transesophageal echocardiography (TEE) [3].

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography combined with computed tomography (PET/CT) has shown effectiveness in diagnosing infectious diseases. The value of ^{18}F-FDG-PET/CT in diagnosing infective endocarditis has been reported [4] and has shown to be a valuable diagnostic technique in patients suspected of prosthetic valve endocarditis (PVE). Recently, ^{18}F-FDG-PET/CT was added to the European Society of Cardiology modified diagnostic criteria as a major criterion for PVE [5]. In patients with native valve endocarditis (NVE), the diagnostic value of ^{18}F-FDG-PET/CT has not been studied extensively. A few studies, including often less than 10 patients with native valves, found low sensitivity for ^{18}F-FDG-PET/CT in diagnosing NVE [4]. However, these studies were often performed without prior low carbohydrate-fat allowed diet to suppress cardiac glucose metabolism [6]. The purpose of this study was to investigate the diagnostic value of ^{18}F-FDG-PET/CT in NVE in a large cohort of patients, prepared with a low carbohydrate-fat allowed diet.

Methods

Patients and study design

All patients in this study were retrospectively included between January 2013 and June 2016 in the Radboud university medical center, a tertiary referral center in Nijmegen, the Netherlands. Patients with bacteremia were included when both echocardiography, because of suspicion of NVE (TTE and/or TEE), and ^{18}F-FDG-PET/CT were performed within 14 days. Exclusion criteria were an age below 18 years, prosthetic heart valve, cardiac implantable electronic devices (CIED) infections, more than 14 days between ^{18}F-FDG-PET/CT and echocardiography, when no low carbohydrate-fat allowed diet was used prior to the ^{18}F-FDG-PET/CT, and when assessment of the heart was impossible due to physiological ^{18}F-FDG uptake despite the low carbohydrate-fat allowed diet. According to Dutch law, this study was exempt from approval by an ethics committee, because of the retrospective character of this study and the anonymous storage of data. This was confirmed by the regional ethics committee.

In all patients included in this study, the microbiologists advised for an infectious disease specialist consultation because of the positive blood culture. All patients were discussed in a multidisciplinary 'endocarditis team', including infectious disease specialists, medical microbiologists, cardiologists, and nuclear medicine physicians. In this weekly multidisciplinary meeting, the medical history, physical examination, laboratory and microbiological results, and imaging results including ^{18}F-FDG-PET/CT of all patients were presented and based on this clinical information a diagnosis was made. The diagnosis was not based on a scoring system but made by consensus by all physicians present at the meeting based on all clinical signs and symptoms, risk factors, blood cultures (number of positive cultures/total, micro-organism) and all imaging performed. For echocardiography, TTE was used as a first-line screening technique. TEE was advocated in all patients in whom TTE was negative for NVE, especially when imaging was hampered due to technical or anatomical problems. NVE was diagnosed according to the modified Duke criteria [2] as gold standard and also to the multidisciplinary consensus. NVE was treated according to international guidelines [5].

Diagnostic work-up

An integrated PET/CT scanner (Biograph 40 mCT; Siemens Healthcare) was used for imaging. Before ^{18}F-FDG injection, patients fasted and any glucose or insulin-containing infusions were discontinued for at least six hours.

All patients were instructed to adhere to a low carbohydrate-fat allowed diet 24 hours before ^{18}F-FDG-PET/CT was performed. Blood glucose samples were taken from all patients prior to ^{18}F-FDG administration. At the time of ^{18}F-FDG injection glucose was below 12 mmol/l in all patients. One hour after intravenous injection of an average dosage of 3.3 MBq/kg ^{18}F-FDG (Mallinckrodt Pharmaceuticals, Petten, The Netherlands or IBA Molecular, Amsterdam, The Netherlands), a whole-body low-dose CT scan was acquired for anatomic correlation and attenuation correction of the PET data. Emission images of the same area were acquired. Images of the heart were re-evaluated independently by two nuclear medicine physicians without knowledge of prior clinical evaluation. When it was not possible to reliably evaluate the valve planes, patients were excluded. Any increased ^{18}F-FDG uptake in or around the heart valves outside the area of the myocardium was considered as abnormal. Minimally increased ^{18}F-FDG uptake was defined as uptake in the region of a heart valve just above normal heart uptake. Highly increased ^{18}F-FDG uptake of a heart valve was defined as uptake in the region of the heart valve clearly distinguishable from normal heart uptake. When uptake in the region of a heart valve was not distinguishable from normal heart uptake, ^{18}F-FDG uptake was considered negative. Subsequently, discordant results were solved by consensus reading.

Echocardiography was considered positive for infective endocarditis when vegetations, defined as oscillating intracardiac structures, were visualized on the valves or their adjacent structures or in the path of a regurgitant jet in the absence of an alternative anatomic explanation.

Statistical analysis

In patients with definite NVE according to the modified Duke criteria, any comparison was made with patients with possible and rejected NVE according to the modified Duke criteria. The kappa statistic test was used to calculate the level of agreement between the two nuclear medicine physicians. Differences in outcomes were tested using Fisher's exact test for categorical variables. Statistical significance was defined as a *p* value less than 0.05. Statistical analysis was performed using SPSS (version 22.0;SPSS, Inc.).

Results

A total of 104 patients underwent both echocardiography and ^{18}F-FDG-PET/CT within 14 days because of bacteremia. Sixteen patients were excluded because ^{18}F-FDG-PET/CT scan quality was too limited for assessment of the heart region because of physiological ^{18}F-FDG uptake. Of all 88 included patients, baseline characteristics are shown in Table 1. Ten patients (11.4%) were diagnosed with definite NVE and 48 patients (54.5%) were diagnosed with possible NVE according to the modified Duke criteria. In 30 patients, diagnosis of NVE was rejected (34.1%). The evaluation of ^{18}F-FDG-PET/CT for NVE showed a high level of agreement (Cohen's kappa 0.97).

Definite NVE

In 10 patients with definite NVE according to the modified Duke criteria, 3 patients (30.0%) had increased ^{18}F-FDG uptake in or around the heart valves. Seven patients (70.0%) had no increased ^{18}F-FDG uptake in or around the heart valves. In patients without definite NVE according to the modified Duke criteria, 89.7% (70/78) patients had no increased ^{18}F-FDG uptake in or around the heart valves. In all patients with definite NVE according to the modified Duke criteria and with increased ^{18}F-FDG uptake at the heart valve region, ^{18}F-FDG uptake was highly increased.

Possible NVE

Of all 48 patients with possible NVE according to the modified Duke criteria, 5 patients (10.4%) had increased ^{18}F-FDG uptake in or around the heart valves. Although these 5 patients had only possible NVE according to the modified Duke criteria, 3 of these patients (60.0%) were treated as having NVE based on the severity of infection, risk factors, and ^{18}F-FDG-PET/CT results (Fig. 1). Of 43 patients with possible NVE according to the modified Duke criteria without increased ^{18}F-FDG uptake in the heart valve region, 4 patients (9.3%) were treated as having NVE.

Rejected NVE

In 3 patients with increased ^{18}F-FDG uptake in the heart valve region, NVE was rejected according to the Duke criteria. One patient was treated for 2 years until his death for an infected abdominal aortic graft with *E. coli* and *C. albicans.* Another patient was treated for 6 months until her death for an infected thoracic aortic aneurysm

with *Salmonella dublin*. One patient was treated for 6 weeks because of *S. aureus* bacteremia with metastatic foci in lungs and soft tissue. She died 6 months later due to duodenum carcinoma.

Multidisciplinary consensus

NVE was diagnosed according to the multidisciplinary consensus in 20 patients (22.7%) (Fig 2). Of all patients with NVE according to the multidisciplinary consensus, 9 patients (45.0%) had increased ^{18}F-FDG uptake in or around the heart valves and 11 patients (55.0%) had normal ^{18}F-FDG-PET/CT. Of the 20 patients with definite NVE according to the multidisciplinary consensus, 10 were initially classified as definite, 7 as possible, and 3 as rejected endocarditis by the modified Duke criteria. In patients with increased ^{18}F-FDG uptake in or around the heart valves, metastatic infection other than endocarditis was found in 72.7% (8/11) of patients and in patients without increased ^{18}F-FDG uptake in or around the heart valves metastatic infection was found in 51.9% (40/77) of patients (p = 0.195). No relapses occurred.

Classification of all patients according to the diagnosis of NVE based on the modified Duke criteria, modified Duke criteria including ^{18}F-FDG-PET/CT result as a major criterion, ^{18}F-FDG-PET/CT result only, and diagnosis according to the multidisciplinary consensus are shown in Table 2.

Metastatic infection

^{18}F-FDG-PET/CT detected metastatic infection other than endocarditis in 48 patients (54.5%). ^{18}F-FDG-PET/CT was the first modality to localize infectious foci in 38 patients (79.2%). Localizations of these metastatic infection were endovascular infection (23.7%), spondylodiscitis (23.7%), pulmonary foci (15.8%), arthritis (13.2%), soft tissue infections (13.2%), splenic abscesses (7.9%), and non-vertebral osteomyelitis (2.6%).

Discussion

Data on the value of ^{18}F-FDG-PET/CT in NVE is limited. This is the first study in a large cohort investigating the value of ^{18}F-FDG-PET/CT in patients with suspected NVE only, by excluding PVE and CIED infections. Our study shows that ^{18}F-FDG-PET/CT has a low sensitivity with 7 out of 10 patients with definite NVE according to the modified Duke criteria without increased ^{18}F-FDG uptake of the heart valve. Although ^{18}F-FDG-PET/CT is insufficient to rule out NVE, a positive finding on ^{18}F-FDG-PET/CT is sufficiently specific to imply clinical consequences, as 70 out of 78 patients without definite NVE according to the modified Duke criteria showed no increased ^{18}F-FDG uptake around the heart valves. The results of our study are in line with three other studies performed on the value of ^{18}F-FDG-PET/CT in NVE. These studies, mainly focusing on PVE with inclusion of only 6 [7] and 7 [8,9] patients with NVE, found very low sensitivity for ^{18}F-FDG-PET/CT in NVE. Previously, we performed a prospectively included study on the value of ^{18}F-FDG-PET/CT in 72 patients with suspected endocarditis of whom 66 patients had suspected NVE [10]. In this study, an older generation PET/CT scanner was used and no low carbohydrate-fat allowed diet was performed. In the present study, the level of agreement between two evaluating nuclear medicine physicians was much higher than in the previous study (0.97 versus 0.36). This difference is probably explained by the increasing experience in evaluating ^{18}F-FDG-PET/CT in NVE since this previous study and our multidisciplinary meeting performed weekly since 2013.

NVE is a clinical diagnosis that is based on risk factors, physical examination, microbiological results, and imaging. The fact that diagnosing NVE is challenging, is shown by the limited sensitivity of the modified Duke criteria [2], which remain the 'gold standard' for diagnosis. Also, a large percentage of suspected NVE cases remains as possible NVE [11]. Therefore, patients with suspected NVE should be discussed in a multidisciplinary endocarditis team, to incorporate as much individualized information as possible in the final diagnosis. Our results show that by multidisciplinary consensus definite NVE was diagnosed twice as often compared to diagnosis according to the modified Duke criteria and also the discouraging diagnosis of possible NVE was abandoned. ^{18}F-FDG-PET/CT is an imaging technique that should be assessed within the clinical context of patients. Reevaluation of ^{18}F-FDG-PET/CT without knowledge of clinical details which is common in this type of studies, could lead to less sensitive reading.

The diagnostic value of ^{18}F-FDG-PET/CT for PVE has been extensively studied with promising results [4] and ^{18}F-FDG-PET/CT was recently added to the European Society of Cardiology modified diagnostic criteria for PVE [5]. Because of its relatively high specificity, adding ^{18}F-FDG-PET/CT to the Duke criteria also for NVE could be valuable, as our results show an increase of NVE diagnoses when ^{18}F-FDG-PET/CT is included (Table 2). Three patients with rejected NVE according to the modified Duke criteria and increased ^{18}F-FDG uptake of the heart valves were at high risk for NVE and could have been incorrectly diagnosed as rejected NVE. The fact that TTE only, and thus no TEE, was performed in the majority of patients with possible or rejected NVE (Table 1), could have led to missed diagnoses of definite NVE. The diagnostic criteria of the European Society of Cardiology from 2015 recommends cardiac CT in suspected NVE [5]. In our study, we did not perform cardiac CT as part of our diagnostic protocol in NVE, partly due to the fact that patients were included from 2013 in the present study.

Besides intra-cardiac lesions, the value of ^{18}F-FDG-PET/CT has been studied on extra-cardiac complications of endocarditis. ^{18}F-FDG-PET/CT has proven to be valuable and cost-effective in detecting metastatic foci in patients with bacteremia and PVE and/or NVE [12,13,14] and is therefore increasingly used in patients with suspected endocarditis. In our study, metastatic infection other than endocarditis was detected by ^{18}F-FDG-PET/CT in 54.5% of patients, which is comparable to previous results [13,14].

A possible explanation for the limited sensitivity of ^{18}F-FDG-PET/CT in diagnosing NVE is continuous movement of the cardiac valves during acquisition and the small size of vegetations, as metabolism in very small vegetations could be insufficient to be discernible above background activity, especially after being blurred by the movement of the heart [5]. Also, in the subacute-chronic phase of vegetations, microorganisms may disappear and granulomatous inflammation occurs with transformation of vegetations into calcified deposits [15]. So, a subacute course of NVE could decrease the sensitivity of ^{18}F-FDG-PET/CT as ^{18}F-FDG accumulates particularly in activated leukocytes. Gomes et al. [4] proposed a diagnostic algorithm in suspected infective endocarditis. The authors state that patients with highly suspected NVE should undergo both TEE and MDCTA (electrocardiogram-gated multidetector CT angiography) to image intra-cardiac lesions, and also ^{18}F-FDG-PET/CT for detecting extra-cardiac foci and for intra-cardiac lesions in case of sustained suspicion of NVE after inconclusive TEE and MDCTA. ^{18}F-FDG is not a specific tracer, as ^{18}F-FDG uptake could also increase in atherosclerotic plaques in the heart or physiological uptake in the myocardium and papillary muscles. Leukocyte

scintigraphy with SPECT/CT is known for a high specificity in detection of infectious foci and its value has been investigated in PVE and CIED infection [16,17]. More specific PET/CT tracers, additional heparin preadministration [6], motion correction, ECG-gated scanning, respiratory gated scanning to reduce breathing motion artifacts, and/or combination with MDCTA, potentially optimize the diagnostic performance of PET/CT to detect NVE.

Limitations of this study are the retrospective study design and the small number of patients with definite native valve endocarditis according to the modified Duke criteria. In our cohort of 88 patients, 48 patients were classified as possible NVE according to the modified Duke criteria. However, despite these small number of patients with definite NVE this is the largest study so far on patients with native valve endocarditis. Due to our study design, the comparison between ^{18}F-FDG-PET/CT and the multidisciplinary consensus could have led to incorporation bias, due to the fact that ^{18}F-FDG-PET/CT is a part of the multidisciplinary consensus.

In conclusion, a negative ^{18}F-FDG-PET/CT result should not be interpreted as an exclusion of NVE. In patients with possible or rejected NVE according to the modified Duke criteria, ^{18}F-FDG-PET/CT could be used in case of sustained suspicion of NVE due to its high specificity in case of abnormal FDG-uptake at the valve region. In patients suspected of NVE, ^{18}F-FDG-PET/CT is important for detecting metastatic infection which already warrants the need to perform ^{18}F-FDG-PET/CT in all patients with NVE.

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Figures

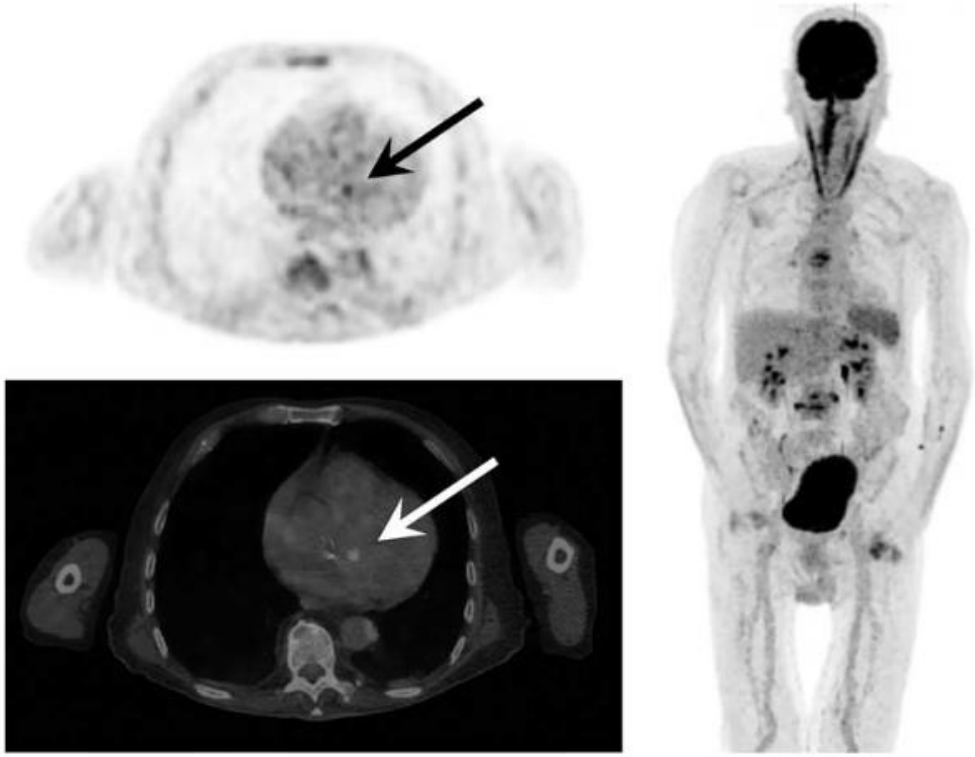

Fig. 1 ^{18}F-FDG-PET/CT images of a 79-year-old man who was admitted with fever and positive blood cultures with *Streptococcus gallolyticus*. Besides spondylodiscitis of Th8-9 and L3-4, ^{18}F-FDG-PET/CT showed increased ^{18}F-FDG uptake of the mitral valve (arrow). TEE was negative for endocarditis. Although this patient had only possible endocarditis according to the modified Duke criteria, he was treated as having NVE

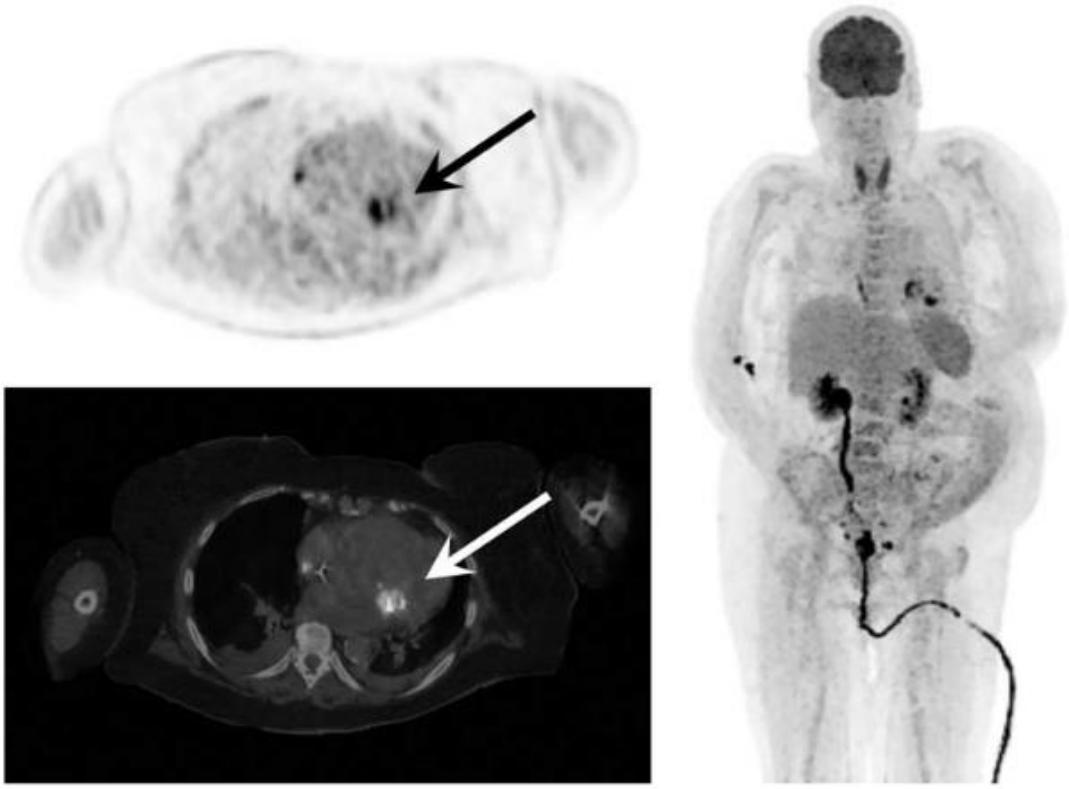

Fig. 2 ^{18}F-FDG-PET/CT images of a 75-year-old woman with a pacemaker and ovarian carcinoma who was admitted with fever and severe confusion. Blood cultures grew *Proteus mirabilis*. TEE was negative for endocarditis. ^{18}F-FDG-PET/CT showed highly increased ^{18}F-FDG uptake of the mitral valve (arrow). A few days later she developed splinter hemorrhages on her hand and foot. TEE was repeated one week after the ^{18}F-FDG-PET/CT and confirmed the diagnosis of native mitral valve endocarditis, no vegetations were seen on her pacemaker leads. This patients died one week later due to therapy-resistant mitral valve endocarditis

Tables

Table 1. Baseline characteristics of all 88 patients with definite, possible, and rejected NVE according to the modified Duke criteria

	Definite endocarditis	Possible endocarditis	Rejected endocarditis
Number of patients	10	48	30
Male (%)	6 (60.0)	28 (58.3)	16 (53.3)
Mean age in years (range)	68.9 (35 - 90)	63.4 (21 - 88)	54.5 (17 - 88)
Blood culture positive (%)	10 (100)	48 (100)	30 (100)
S. aureus (%)	3 (30.0)	40 (83.3)	13 (43.3)
Coagulase-negative Staphylococcus (%)	0	1 (2.1)	1 (3.3)
Streptococcus (%)	5 (50.0)	5 (10.4)	3 (10.0)
Enterococcus (%)	2 (20.0)	1 (2.1)	1 (3.3)
Gram-negative (%)	0	1 (2.1)	10 (33.3)
Other (%)	0	0	2 (6.7)
Pacemaker (%)	2 (20.0)	4 (8.3)	0
ICD [1] (%)	0	1 (2.1)	0
Echocardiography			
TTE [2] only (%)	2 (20.0)	19 (39.6)	23 (76.7)
TEE [3] only (%)	3 (30.0)	2 (4.2)	2 (6.7)
Both TTE and TEE (%)	5 (50.0)	27 (56.3)	5 (16.7)
Metastatic infection other than endocarditis (%)	8 (80.0)	30 (62.5)	10 (33.3)

[1] ICD: implantable cardioverter defibrillator.

[2] TTE: transthoracic echocardiography.

[3] TEE: transesophageal echocardiography

Table 2. Diagnosis of NVE according to the modified Duke criteria, the modified Duke criteria including ^{18}F-FDG-PET/CT, revised ^{18}F-FDG-PET/CT result only, and diagnosis by multidisciplinary consensus

	Modified Duke criteria (%)	Modified Duke criteria including ^{18}F-FDG-PET/CT (%)	Revised ^{18}F-FDG-PET/CT result only (%)	Multidisciplinary consensus[1]
(n=88)				
Definite	10 (11.4)	18 (20.5)	11 (12.5)	20 (22.7)
Possible	48 (54.5)	43 (48.9)	0	0
Rejected	30 (34.1)	27 (30.7)	77 (87.5)	68 (77.3)

[1] Multidisciplinary board including infectious diseases specialists, medical microbiologists, cardiologists, nuclear medicine physicians, and if needed cardiac surgeons.