Infections in patients using ventricular-assist devices: Comparison of the diagnostic performance of ^{18}F-FDG PET/CT scan and leucocyte-labeled scintigraphy

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Background. **The usage of left-ventricular-assist device (LVAD) is increasing in patients presenting with advanced heart failure. However, device-related infections are a challenge to recognize and to treat, with an important morbidity and mortality rate. The role of nuclear medicine imaging remains not well established for LVAD infections. The present study compared the accuracy of positron emission tomography/computed tomography with ^{18}F-fludeoxyglucose (^{18}F-FDG PET/CT) and radiolabeled leucocyte scintigraphy for the diagnosis of infections in patients supported with a continuous-flow LVAD.**

Methods. **From a prospectively maintained database, we retrospectively analyzed the diagnostic performance of radiolabeled leucocyte scintigraphy and ^{18}F-FDG PET/CT in 24 patients who had a LVAD with a suspected device-related infection. Both examinations were routinely performed in all patients. Infection was assessed by the International Society for Heart and Lung Transplantation criteria.**

Results. **Twenty-four patients were included: 15 had a specific VAD infection (5 cardiac-LVAD and 10 driveline), 6 had a VAD-related infection, while 3 patients had a non-VAD-related infection. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 95.2%, 66.7%, 95.2%, 66.7%, and 91.6%, respectively, for ^{18}F-FDG-PET; and 71.4%, 100%, 100%, 33.3%, and 75%, respectively, for leucocyte scintigraphy. ^{18}F-FDG PET/CT showed significantly higher sensitivity (P=0.01) than leucocyte scintigraphy.**

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Conclusion. **^{18}F-FDG PET/CT and radiolabeled leucocyte scintigraphy single-photon emission computed tomography carry high performance in the diagnostic of LVAD infections. ^{18}F-FDG PET/CT shows significantly higher sensitivity and could be proposed as first-line nuclear medicine procedure. (J Nucl Cardiol 2019;26:42–55.)**

Spanish Abstract

Antecedentes. **El uso de dispositivos de asistencia ventricular izquierda (DAVI) está incrementando en pacientes con insuficiencia cardiaca avanzada. Sin embargo, las infecciones relacionadas al dispositivo representan un reto diagnóstico y de tratamiento, con una importante tasa de morbilidad y mortalidad. El papel de los estudios de imagen de medicina nuclear en las infecciones de DAVI no se ha establecido claramente. El presente estudio comparó la precisión de la tomografía por emisión de positrones/tomografía computada con ^{18}F-fluorodesoxiglucosa (^{18}F-FDG PET/CT) y la gammagrafía con leucocitos marcados para el diagnóstico de infecciones en pacientes utilizando un DAVI de flujo continuo.**

Métodos. **Desde una base de datos obtenida de manera prospectiva, analizamos de manera retrospectiva el rendimiento diagnóstico de la gammagrafía de leucocitos marcados y del ^{18}F-FDG PET/CT en 24 pacientes quienes tenían un DAVI con sospecha de infección relacionada al dispositivo. Ambos estudios fueron realizados rutinariamente en todos los pacientes. Se determinó la presencia de infección mediante los criterios de la ISHTL.**

Resultados. **Se incluyeron veinticuatro pacientes, de los cuales 15 tuvieron una infección específica de DAV (5 con infecciones DAVI, y 10 con infección del driveline), 6 tuvieron una infección relacionada al DAV, y 3 pacientes tuvieron una infección no relacionada al DAV. La sensibilidad, especificidad, valor predictivo positivo, valor predictivo negativo y precisión diagnóstica fueron 95.2%, 66.7%, 95.2%, 66.7% y 91.6%, respectivamente para ^{18}F-FDG PET/CT, y 71.4%, 100%, 100%, 33.3% y 75%, respectivamente para la gammagrafía de leucocitos marcados. El ^{18}F-FDG PET/CT mostró una significativa mayor sensibilidad (p=0.01) que la gammagrafía con leucocitos marcados.**

Conclusión. **El ^{18}F-FDG PET/CT y la gammagrafía de leucocitos marcados tienen un alto desempeño en el diagnóstico de infecciones de DAVI. El ^{18}F-FDG PET/CT muestra una significativa mayor sensibilidad y podría ser propuesto como el procedimiento de medicina nuclear de primera línea. (J Nucl Cardiol 2019;26:42–55.)**

Chinese Abstract

背景. 左心室辅助装置 **(LVAD)** 越来越多的应用于重度心力衰竭患者。然而, 设备相关的感染有着重要的发病率和死亡率, 并且对其诊断和治疗均是一项挑战。对于 **LVAD** 相关感染, 核医学影像可扮演的角色一直没有完善。本研究针对装备有连续流式 **LVAD** 的感染病人,对比了 **^{18}F-FDG PET/CT** 造影术和放射性标记白细胞闪烁扫描法对感染诊断的准确性。

方法. 从一个前瞻性的数据库, 入选了**24**名疑似设备感染的 **LVAD** 病人, 并回顾性的分析了放射性标记白细胞闪烁扫描法和 **^{18}F-FDG PET/CT** 的诊断表现。所有病人都常规进行了上述两种检查。利用 **ISHLT** 标准对感染情况进行评估。

结果. 在入选的 **24** 名病人中, **15** 名有明确的 **VAD** 感染 **(5** 名心脏的 **LVAD** 和 **10** 名动力传动系统装置**), 6** 名有 **VAD** 相关的感染,另外**3**名有 **VAD** 无关的感染。对于 **^{18}F-FDG PET/CT** 诊断方法,其敏感性,特异性,阳性预测值,阴性预测值和准确率分别为: **95.2%, 66.7%, 95.2%, 66.7%,** 和 **91.6%;** 而对于白细胞闪烁扫描诊断方法, 其敏感性, 特异性, 阳性预测值,阴性预测值和准确率分别为: **71.4%, 100%, 100%, 33.3%** 和 **75%**。相比于白细胞闪烁扫描, **^{18}F-FDG PET/CT** 明显展现出较高的敏感性 **(p=0.01)**。

结论. **^{18}F-FDG PET/CT** 和白细胞闪烁扫描 **SPECT** 对于 **LVAD** 感染的诊断具有很好的表现。**^{18}F-FDG PET/CT** 展现出较高的敏感性,可以作为核医学的首要检查。 **(J Nucl Cardiol 2019;26:42–55.)**

French Abstract

Contexte. **L'utilisation du dispositif d'assistance ventriculaire gauche (DAVG) est en utilisation croissante chez les patients avec insuffisance cardiaque avancée. Cependant, les infections**

liées au dispositif sont un défi à reconnaître et à traiter en raison d' un taux de morbidité et de mortalité important. Le rôle de l'imagerie de médecine nucléaire n'est pas encore bien établi pour les infections secondaires au DAVG. La présente étude compare la précision de la tomographie par émission de positrons / tomodensitométrie au 18F-fluorodéoxyglucose (18F-FDG TEP/TDM) et la scintigraphie leucocytaire radio-marquée pour le diagnostic d'infections chez des patients porteurs par un DAVG à flux continu.

Méthodes. **A partir d'une base de données complétée de manière prospective nous avons analysé rétrospectivement les performances diagnostiques de la scintigraphie leucocytaire radio-marquée et de la TEP / TDM au 18F-FDG chez 24 patients ayant un DAVG avec une infection suspectée liée à l'appareillage. Les deux types d'examens scintigraphiques ont été systématiquement réalisé chez tous les patients. Le diagnostic d'infection fut établi selon les critères ISHLT.**

Résultats. **Parmi les 24 patients inclus, 15 avaient une infection spécifique de l'appareillage AVG (5 au niveau de la pompe et/ou canule d'insertion myocardique) et 10 au niveau du driveline, 6 avaient une infection indirectement liée à l'appareillage AVG, tandis que 3 patients avaient une infection non liée au DAVG. La sensibilité, la spécificité, la valeur prédictive positive, la valeur prédictive négative et la précision étaient de 95,2%, 66,7%, 95,2%, 66,7% et 91,6%, respectivement, pour le 18F-FDG-PET et 71,4%, 100%, 100%, 33,3 %, et 75%, respectivement, pour la scintigraphie leucocytaire. La TEP / TDM au 18F-FDG a montré une sensitivité significativement plus élevée (p = 0,01) que la scintigraphie leucocytaire.**

Conclusion. **18F-FDG TEP/TDM et scintigraphie leucocytaire radio-marquée SPECT s'avèrent très efficaces pour le diagnostic des infections à DVAG. La TEP/TDM au 18F-FDG montre une sensibilité significativement plus élevée et pourrait être proposée en tant que la procédure de médecine nucléaire de premier choix. (J Nucl Cardiol 2019;26:42–55.)**

Key Words: Infection · PET · SPECT · image interpretation

Abbreviation	
LVAD	Left-ventricular-assist device
VAD	Ventricular-assist device
DL	Driveline
CIED	Cardiac-implantable electronic device
^{18}F-FDG	^{18}F-fludeoxyglucose positron
PET/CT	emission tomography/computed tomography
ISHLT	International Society for Heart and Lung Transplantation
EANM	European Association of Nuclear Medicine
HMPAO	Hexamethylpropyleneamine oxime
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
MR	Magnetic resonance
CT	Computed tomography
SPECT	Single-photon emission computed tomography
ROC	Receiver operating characteristics
SUV	Standard uptake value
MBP	Mediastinal blood pool
WBC	White blood cell

See related editorial, pp. 56–58

INTRODUCTION

Heart failure is a common and serious disease, with a high mortality rate, accounting for more than 4 million deaths of people each year in Europe.[1] Although the incidence of heart failure continues to increase, there is a constant shortage of donor organs, overcome by the improvement and expanding use of left-ventricular-assist device (LVAD), implanted as bridge-to-transplant or destination therapy (i.e., alternative to transplantation). Despite technical improvements of LVAD (particularly the advent of newer generation continuous-flow-assist devices), infections represent a major limitation to the successful use of VAD, leading to a high mortality rate. Between 2012 and 2014, the seventh Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report[2] recorded an infection rate of 7.3 events/100 patients months in the first 12 months post implant for continuous-flow LVAD and biventricular-assist device (N=12,030).

Identifying LVAD infections is a challenge, as echocardiography shows low diagnostic value in infectious endocarditis on cardiac-implantable electronic devices (CIEDs), even with transoesophageal

echocardiography,[3] and magnetic resonance (MR) is largely precluded. On the other hand, computed tomography (CT)-scan is particularly useful, especially in assessing cannulas, thrombi, vegetations, or sternal wound infections. Nuclear imaging has potential value in the diagnostic strategy of LVAD and CIED infections, but only few studies have evaluated the diagnostic efficacy of ^{18}F-fludeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) imaging[4-8] and leucocyte-labeled scintigraphy,[9,10] and there is still no consensus criteria for interpretation of these two techniques. Very little is known about the diversity of LVADs (different types and trends, new generation of continuous-flow devices) and their different material compositions (areas of Dacron, GoreTex) by physicians. Keidar et al[11] showed that increased ^{18}F-FDG activity may occur in the absence of an acute infectious process, and that grafts often induce a foreign-body chronic low-grade inflammatory reaction, which can also exhibit increased ^{18}F-FDG activity, and induce erroneous interpretation of ^{18}F-FDG PET/CT. This chronic inflammatory phenomenon occurs frequently around the Dacron area and should therefore be known as a source of interpretation pitfalls.

The main objective of this study was to compare the respective performances of ^{18}F-FDG PET/CT and leucocyte scintigraphy in the diagnosis LVAD infections. Our secondary objective was to evaluate the respective performances of visual and quantitative ^{18}F-FDG PET/CT interpretation scales.

MATERIALS AND METHODS

Patient Population

This monocentric retrospective study included patients who had undergone both radiolabeled leucocyte scintigraphy single-photon emission computed tomography (SPECT) and ^{18}F-FDG PET/CT for a suspected infection of LVAD between April 2013 and July 2017. The patients underwent routinely both examinations systematically and independently, regardless the results of each imaging. The median time between both examinations was 3 days. Suspicion of a VAD-related infection could be based on the patient's clinical history, clinical symptoms, biology, or imaging. Antibiotherapy was introduced when deemed necessary. Clinical signs, demographic, biological, and imaging data were recorded for each patient (Table 1).

Case Definition of LVAD-Related Infection

LVAD-related infection was diagnosed according to the International Society for Heart and Lung Transplantation (ISHLT) criteria for infection in patients using VADs.[12] The patients were therefore divided into three categories defined as follows:

- *VAD-specific infections* pump and/or cannula infections, pocket infections, percutaneous driveline (DL) infections (both superficial and deep infections);
- *VAD-related infections* infective endocarditis, bloodstream infections (BSIs) [including central venous catheter (CVC) and/or BSIs], Mediastinitis VAD-related or non-VAD-related (other causes of mediastinitis, perforation of the esophagus); and
- *Non-VAD infections* lower respiratory tract infection, cholecystitis, *Clostridium difficile* infection, urinary tract infection.

As there are different types of LVAD (Heartmate II, Heartware, Jarvik 2000), the cardiac-LVAD category included pump, canula, and pocket infections. The material was considered infected or not according to ISHLT criteria applied at the end of the follow-up, and based on clinical symptoms, biology, and, if positive, imaging data (echocardiography, CT). In case of missing data to conclude on the infectious status, the final diagnosis was specified by the multidisciplinary consensus meetings.

Radiolabeled Leucocyte Scintigraphy SPECT Protocol

Autologous radiolabeled white blood cells (WBCs) were prepared and separated according to European Association of Nuclear Medicine (EANM) guidelines and according to the characteristics of Ceretec® for the labeling of neutrophils with technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO).[13] Radiolabeling efficiency was always in the range of 70%-85%. Whole-body and spot planar images were obtained after 30 minutes, then 2 or 4-6 hours (delayed images) and 20-24 hours (late images) after reinfusion of 148-555 MBq (megabecquerel) of ^{99m}Tc-HMPAO WBC. SPECT of the region of interest was performed in all patients at the end of 4 hours and repeated at 24 hours. Images were acquired using a dual-head, variable-angle SPECT γ camera (Hawkeye and Discovery ST; GE Healthcare). A low-dose CT transmission scan was acquired for 16 seconds over 220° for each transaxial slice. The full field of view consisting of 40 slices was completed in 10 minutes. CT scans were reconstructed into a 256×256 matrix. SPECT component of the same field of view was acquired using a 128×128 matrix, 360° rotation, and acquisition times of 40 and 60 seconds per frame at 2-4 and at 24 hours, respectively. Both CT attenuation-corrected and noncorrected SPECT images were evaluated in the coronal, transaxial, and sagittal planes, as well as in tridimensional maximum intensity projection cine mode. Matching pairs of x-ray transmission and radionuclide emission images were fused using Xeleris™ software (GE Healthcare), and hybrid images of overlying transmission and emission data were generated.

^{18}F-FDG PET/CT Protocol

Patients received a low-carbohydrate, high-fat meal the day before ^{18}F-FDG PET imaging and were then asked to fast

Table 1. Main baseline characteristics of 24 patients with suspected infection of LVAD

Characteristics	Patients (N = 24)
Sex [N] female/male	3/21
Age [median (IQR2)]	57 (28-78)
LVAD	
Heartmate II	14
Heartware	7
Jarvik 2000	3
Indication of LVAD	
Bridge to transplant	15
Destination therapy	9
Pathology LVAD	
Ischemic cardiopathy	13
Non ischemic dilated cardiopathy	10
Other (congenital anomaly)	1
Comorbidities [N (%)]	
Diabetes mellitus	6
Neoplasm (treatment<2 years)	2
Delay between installation of LVAD and nuclear imaging in days [median (IQR)]	165 [3-1095]
Antibiotic treatment before nuclear imaging [N (%)]	12 (50)
Antibiotic treatment duration before nuclear imaging in days [median (IQR)]	34.5 [3-210]
Clinical symptoms	21 (87.5)
Fever	8
Purulent issue driveline	11
Abdominal pain	2
Tumefaction on operatory site	1
None	3
Laboratory findings [N/total tested (%)]	
Positive blood cultures	11 (45.8)
Positive pus cutaneous driveline	13 (54.2)
Serum C-reactive protein>10 $mg{\cdot}L^{-1}$	15 (62.5)
C-reactive protein [median (IQR2)]	50 [4-253]
Blood granulocyte count>7.5 G/L	14 (58.3)
Blood granulocyte count (G/L) [median (IQR2)]	7.9 [3.5-13.5]
Heart transplant	9
Periprosthetic purulence found during LVAD explantation	1
Culture positive of LVAD after explantation	5
Deceased patients	5
From septic shock	1
Other cause	4
Final diagnosis	
Non-VAD infection	3
Digestive origin	2
Pulmonary origin	1
VAD-related infection	6
VAD-specific infection	15
Driveline	10
Pump and/or canula infection and/or pocket	5

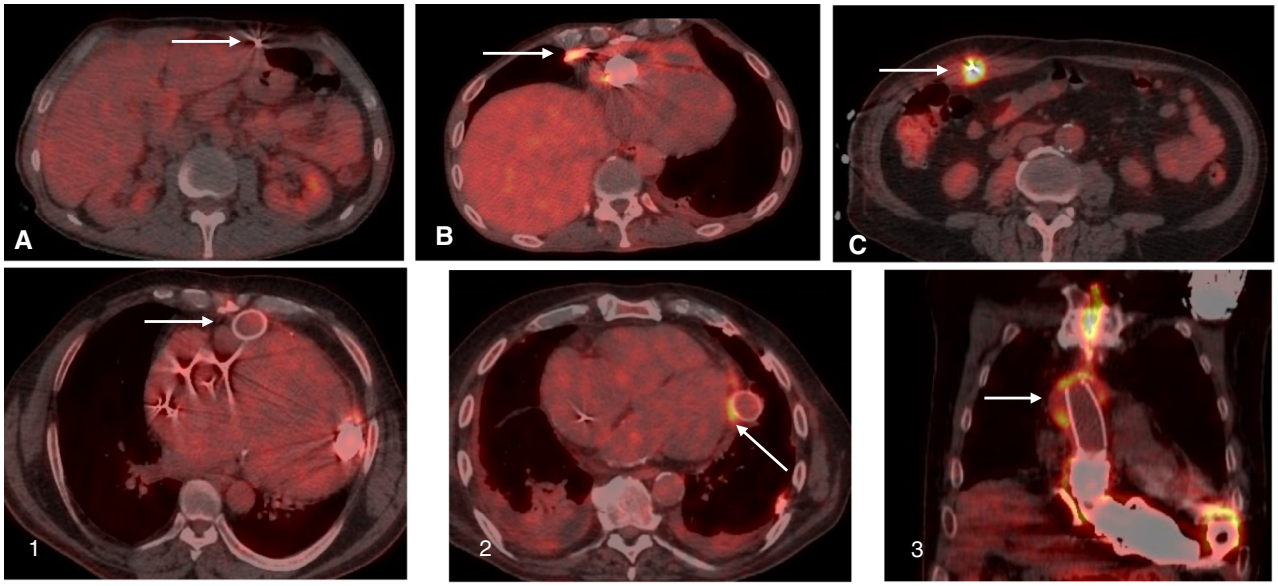

Figure 1. Scale grading scores for the driveline (line 1) and the cardiac-LVAD (line 2). Row 1 grading score for the driveline: (**A**) no uptake, median abdominal portion of the driveline; (**B**) focal or segmentary uptake without extension to soft tissues, proximal portion of the driveline; and (**C**) uptake with extension to soft tissues, median portion of the driveline. Row 2 grading score for the cardiac-LVAD-device: (**1**) no uptake, outflow canula of Heartmate II LVAD (arrow), (**2**) segmentary uptake without extension to soft tissues, axial view of outflow canula of a Jarvik 2000 device, and (**3**) uptake extended to soft tissues, coronal view of pomp, pocket and canulas of a Heartmate II device.

for at least 12 hours to limit physiologic myocardial ^{18}F-FDG uptake. Blood glucose levels were measured prior to the injection of FDG. Patients with blood glucose levels< 9 mmol·L^{-1} were accepted for imaging. Approximatively 3.5 MBq·kg^{-1} of body weight of ^{18}F-FDG was injected intravenously 60 minutes before PET data acquisition (mean activity 310±51 MBq). All scans were performed on an integrated PET/CT system (Discovery VCT or Discovery 690; GE Healthcare, Milwaukee, WI, USA). The CT (5-mm slices, 100-130 kV, and 100-150 mA; median DLP 800 mGy·cm) was carried out without administration of intravenous contrast agent. Images were analyzed on an AW Workstation Version 4.4 (GE Healthcare Biosciences, Pittsburgh, PA, USA).

Image Analysis and Interpretation

Separate readings of ^{18}F-FDG PET/CT and leucocyte scintigraphy were performed by two experienced nuclear medicine physicians, aware of the patient's clinical history, in consensus. For each examination, we divided our analysis into two parts: the analysis of the DL (divided into three portions—proximal, median, and distal), and the analysis of the cardiac-LVAD (regrouping cannulas, pocket, and pump).

Interpretation criteria of ^{18}FDG PET-CT. A visual analysis was performed (Figure 1), defined by three points, applicable to the DL and to the cardiac part of the LVAD. As a diffuse homogeneous ^{18}F-FDG uptake is currently found in noninfected prosthetic vascular grafts[11] because of local inflammatory process, only focal FDG uptake was retained as a positive septic focus for the cardiac part of LVAD.

The scale was graduated as follows.

For the DL material: (A) no FDG uptake, (B) focal or segmental FDG uptake without extension to soft tissues, (C) focal or segmental FDG uptake with extension to soft tissues.

Every result>grade A was considered pathologic.

For the cardiac part of the LVAD, (1) no uptake or circumferential FDG uptake corresponding to Dacron or GoreTex areas only, (2) focal FDG uptake without extension to soft tissues, and (3) focal or segmental FDG uptake with extension to soft tissues or extending to a mediastinal collection (Figure 2).

Every result>grade 1 was considered pathologic.

Every FDG uptake had to be present on both attenuation-corrected and uncorrected acquisitions, in order to avoid overcorrection artifacts.

Every pathologic ^{18}F-FDG uptake was measured semi-quantitatively as maximum standard uptake value (SUV_{max}). SUV_{max} values of pathologic foci, liver, and mediastinal blood pool (MBP; region of interest drawn in superior vena cava) were also collected for each patient.

Interpretation criteria of leucocyte-labeled scintigraphy. Scintigraphy results were classified as positive when foci of labeled leucocyte uptake greater than background activity were detected in the cardiac area or along the DL and/or when contrast between these foci and

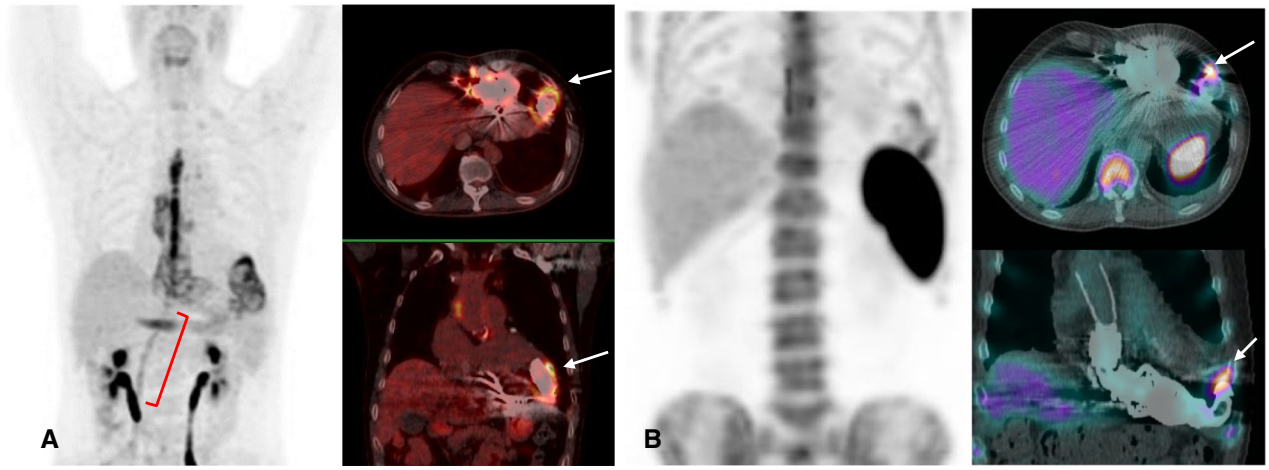

Figure 2. Example of a specific infection of the cardiac-LVAD-device. (**A**) ^{18}F-FDG PET/CT scan showing an intense segmentary uptake on the two canulas of a Heartmate II, with an extension to soft tissues around inflow and outflow canulas (white arrows, axial and coronal views). The uptake on the sternotomy site was considered aspecific. Segmentary uptake classified as grade B is visible along the driveline (3D view, red curved arrow). (**B**) Leucocyte-labeled scintigraphy showing a segmentary uptake on outflow canula (white arrows, axial and coronal views). These findings were visible on both corrected and uncorrected for attenuation acquisitions. Note that there was no fixation visible along the driveline on the leucocyte scintigraphy. The patient presented fever and purulent drainage at the exit site of the driveline, without germ found at pus analysis or hemoculture. The patient had a heart transplant 2 months after the beginning of symptoms. The culture of the Heartmate II device was positive to *Propionibacterium acnes* (patient #2).

background signal increased over time. Foci of nonphysiologic abnormal uptake that decreased after 24 hours were considered negative.

Statistical Analysis

Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were calculated for SPECT and for different ^{18}F-FDG PET/CT reading scales. For the quantitative scale, a receiver operating characteristic (ROC) analysis was performed for determination of threshold values and for calculation of the diagnostic performance. Sensitivity, specificity, were compared using McNemar χ^2 test. Predictive positive and negative values were compared using the generalized score statistic proposed by Leisenring et al[14]. P values<0.05 were considered statistically significant. Statistical analyses were performed using R software.

RESULTS

Clinical Characteristics

Twenty-two patients with LVAD had 24 ^{18}F-FDG PET/CT scan and leucocyte scintigraphy for a suspected infection. Two patients underwent ^{18}F-FDG PET/CT scan and leucocyte scintigraphy twice, with independent clinical presentation and bacteriological results between their two stays in the Nuclear Medicine Department. They were therefore considered as independent cases. Median time between ^{18}F-FDG PET/CT and SPECT was 3 days, with no change in antimicrobial therapy and no surgery during this period. Both examinations were routinely performed as soon as possible, without order of priority, independently of their respective results.

Broad antibiotic treatment was initiated in all patients after the onset of infection and diagnostic measurements, and was adjusted by clinical presentation and antimicrobial susceptibility testing. Baseline characteristics are reported in Table 1.

Infectious Status Groups

VAD-specific infections. 15 patients were classified as having VAD-specific infections:

- Five as pump and/or canula infections, with positive microbiology culture at explantation. Among these patients, four (80%) had also positive blood culture before LVAD explantation.
- Ten as superficial VAD-specific percutaneous DL infections, with positive culture of purulent issue around the exit site of the DL. One patient presented only cutaneous ulcer at DL exit site. No surgical debridement was performed.

Table 2. Diagnostic performance of PET/CT and leucocyte scintigraphy

	Sensitivity	Specificity	PPV	NPV	Accuracy
^{18}F-FDG PET/CT visual analysis	95.2 (20/21)	66.7 (2/3)	95.2 (20/21)	66.7 (2/3)	91.6 (22/24)
^{18}F-FDG PET/CT quantitative analysis	90 (19/21)	66.7 (2/3)	95 (19/20)	50 (2/4)	87.5 (21/24)
SPECT	71.4 (15/21)	100 (3/3)	100 (15/15)	33.3 (3/9)	75 (18/24)

VAD-related infections. 6 patients were classified as having VAD-related infections:

- One patient presented repeat blood cultures positive for *Staphylococcus aureus*, with fever and local pain. Ultrasound imaging and CT found a purulent collection at the surgical site, corresponding to a VAD-related mediastinitis (patient #10).
- The repeat blood cultures of five patients were found to be positive to *Pasteurella multicoda*, *Klebsiella pneumoniae* (two patients), *Streptococcus oralis*, and *Enterococcus faecalis* (two patients). They all had fever>38 °C. No patient presented symptoms of respiratory or digestive infections.

Non-VAD infections. 3 patients were classified as having non-VAD-related infections:

- 1 patient (patient #23) presented a severe respiratory sepsis before the implantation of the Heartmate II, with blood culture, tracheal suction and arterial line culture positive for *S. aureus.* The LVAD was implanted under cover of antibiotics. Despite three different lines of antibiotherapy, and pleural effusion draining, the patient presented a recurrent fever 2 months later. The CT showed an aspect of bilateral infectious pneumonitis. There was no purulent issue at the exit site of the DL and no BSI detectable after the implantation of the LVAD.
- 1 patient presented a cholecystitis asserted by US imaging, with blood culture positive for *Escherichia coli* (patient #24).
- 1 patient had a surgery for colorectal cancer, 1 year after the implantation of his Heartware, with positive blood culture to *E. faecalis* few days after the surgery (patient #22).

Performance of ^{18}F-FDG PET/CT

Visual analysis. Based on visual analysis, ^{18}F-FDG PET/CT accuracy was 91.6%, with sensitivity, specificity, predictive positive value, and predictive negative value of 95.2%, 66.7%, 95.2%, and 66.7%, respectively. PET/CT and leucocyte scintigraphy results are presented in Table 2.

PET/CT examination results were positive in 20 patients out of the 21 patients with VAD-specific or VAD-related infection.

One patient had false-negative PET/CT examination results, with clinical evidence of infection (patient #16; Table 3). This patient had a septic shock a few days after the implantation of a Heartware in bridge-to-transplant. Blood cultures as well as CVC culture were positive to *E. faecalis*. The patient was considered as having a VAD-related infection. ^{18}F-FDG PET/CT and leucocyte scintigraphy were performed 30 days after the initiation of antibiotics and 33 days after the implantation of the LVAD. Both examinations were negative.

One patient presented a lower respiratory tract infection (non-VAD-related, Figure 3, patient #23; Table 3).^{18}F-FDG PET/CT and leucocyte scintigraphy were performed 60 days after the initiation of antibiotics and 61 days after the implantation of the LVAD. An uptake was found along the DL, from the exit of the pump to the abdominal exit site (with a SUV_{max} of 4.2). Leucocyte scintigraphy did not find any uptake on the DL or the cardiac part of the LVAD.

Quantitative analysis. The SUV_{max} of 4.5 was determined from the ROC curve as a cutoff point differentiating positive and negative infection statuses. Using this cutoff, ^{18}F-FDG PET/CT accuracy was 87.5%, with sensitivity, specificity, predictive positive value, and predictive negative values of 90%, 66.7%, 95%, and 50%, respectively.

Comparison of visual and quantitative ^{18}F-FDG PET/CT reading scales. There was no significant difference between visual and quantitative analyses of ^{18}F-FDG PET/CT. Sensitivity, PPV, and NPV were slightly better with visual analysis (95.2%, 95.2%, and 66.7%, respectively) than with quantitative scale (90%, 95%, and 50%, respectively) but did not reach significance (P=0.32, 0.47, and 0.29, respectively). The specificity was the same for both visual and quantitative analyses (66.7%).

Performance of Leucocyte Scintigraphy

Radiolabeled leucocyte scintigraphy SPECT accuracy was 75%, with a sensitivity, specificity, predictive

Table 3. Results of ^{18}F-FDG PET/CT and leucocyte scintigraphy in patients with suspected LVAD infection

Patients	Sex (man/woman), age, type of LVAD	Clinical presentation	Culture results	Antibiotherapy (days)	PET results (visual analysis)	LS results	Infection status
#1	M/48/HM II	PI	Positive blood culture: *Enterobacter cloacae* Purulence issue at DL exit site: *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Staphylococcus haemolyticus* Positive culture of LVAD after explantation: *negative gram Bacillus* (*subculture negative*)	−	+ (DL+C)	−	VAD-specific (pump)
#2	M/58/HM II	Fever, PI	Positive culture of LVAD after explantation: *Propionibacteirum acnes*	−	+ (DL+C)	+ (C)	VAD-specific (pump)
#3	W/59/HM II	PI	Purulence issue at DL exit site: *Pseudomonas aeruginosa*, *Corynebacterium* Positive culture of LVAD after explantation: *Staphylococcus epidermidis*, *negative-coagulase Staphylococcus*	9	+ (DL+C)	+ (DL+C)	VAD-specific (pump)
#4	M/43/HM II	Tumefaction around outflow cannula (CT, US)	Negative	−	+ (DL+C)	+ (DL+C)	VAD-specific (pump)
#5	M/43/HM II	PI	Purulence issue at DL exit site: *Staphylococcus aureus* Positive blood culture: *Staphylococcus aureus* Purulent collection around the HM II (cannulas, pocket and pump) seen at explantation of the LVAD, positive culture: *Staphylococcus aureus*	10	+ (DL+C)	+ (DL+C)	VAD-specific (pump)
#6	M/66/HM II	PI	Purulence issue at DL exit site: *Escherichia coli*, *Citrobacter koseri*, *Enterobacter cloacae*, *Klebsiella oxytoca* Positive culture of LVAD after explantation: *Citrobacter koseri*	−	+ (DL)	+ (DL)	VAD-specific (DL)
#7	M/66/HM II	PI	Purulence issue at DL exit site: *Enterobacter cloacae*	3	+ (DL)	+ (DL)	VAD-specific (DL)
#8	M/54/HW	PI	Purulence issue at DL exit site: *Bacillus cereus*, *Corynebacterium*, *Staphylococcus epidermidis*, *Corynebacterium tuberculostearicum*	−	+ (DL)	+ (DL)	VAD-specific (DL)
#9	M/56/HM II	PI	Purulence issue at DL exit site: *Staphylococcus aureus*	−	+ (DL)	+ (DL)	VAD-specific (DL)
#10	M/71/HM II	Fever, PI	Purulence issue at DL exit site: *Staphylococcus haemolyticus*	210	+ (DL+C)	−	VAD-specific (DL)
#11	M/59/HM II	PI	Purulence issue at DL exit site: *Staphylococcus aureus*	−	+ (DL)	+ (DL)	VAD-specific (DL)
#12	M/58/HW	PI	Purulence issue at DL exit site: *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*	−	+ (DL)	+ (DL)	VAD-specific (DL)

Table 3 continued

Patients	Sex (man/woman), age, type of LVAD	Clinical presentation	Culture results	Antibiotherapy (days)	PET results (visual analysis)	LS results	Infection status
#13	M/72/J	Cutaneous ulcer of driveline exit site	Negative	−	+ (DL)	−	VAD-specific (DL)
#14	M/28/HM II	PI	Purulence issue at DL exit site: *Staphylococcus aureus*	−	+ (DL)	+ (DL)	VAD-specific (DL)
#15	W/41/HW	PI, abdominal pain	Purulence issue at DL exit site: *Staphylococcus aureus*	60	+ (DL)	−	VAD-specific (DL)
#16	M/53/HW	Septic shock	Positive blood culture: *Enterococcus faecalis*	39	−	−	VAD-related
#17	M/60/HW	Fever, PI	- Positive blood culture: *Streptococcus oralis* - Purulence issue at DL exit site: *Corynebacterium*	30	+ (DL)	−	VAD-related
#18	M/78/HM II	Biological inflammatory syndrome of unknown origin, CRP 274 $mg{\cdot}L^{-1}$)	Positive blood culture: *Pasteurella multicoda*	11	+ (DL+C)	+ (DL+C)	VAD-related
#19	W/56/J	Fever	Positive blood culture: *Klebsiella pneumoniae*, *Staphylococcus haemolyticus*	15	+ (DL)	−	VAD-related
#20	M/50/HW	Fever	Positive blood culture: *Staphylococcus aureus*	45	+ (DL+retrosternal collection)	+ (DL+ retrosternal collection)	VAD-related
#21	M/72/J	Fever	Positive blood culture: *Klebsiella pneumoniae*	120	+ (C)	+ (C)	VAD-related
#22	M/52/HW	Sepsis after surgery for colorectal cancer	Positive blood culture: *Enterococcus faecalis*	−	−	−	Non-VAD-related
#23	M/56/HM II	Fever, respiratory symptoms	Positive blood culture: *Staphylococcus aureus* Cytobacteriological sputum: *Staphylococcus aureus*	60	+ (DL)	−	Non-VAD-related (pneumonia)
#24	M/68/HM II	Fever, abdominal pain	Positive blood culture: *Escherichia coli* Cholecystitis documented on CT and echography	−	−	−	Non-VAD-related (cholecystitis)

Type of LVAD: *HW*, Heartware; *HM II*, Heartmate II; *J*, Jarvik 2000; clinical symptoms: *PI*, purulence issue at driveline exit site; *DL*, driveline; infection status: +, positive; −, negative; *C*, cardiac part of LVAD (pump, cannula, pocket); *DL*, driveline

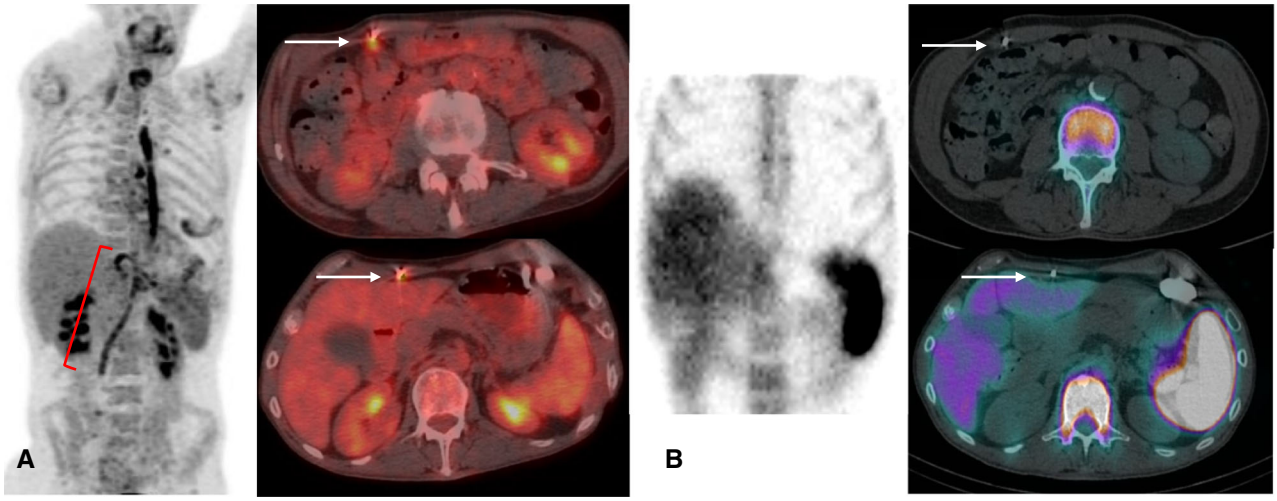

Figure 3. Example of discordance between ^{18}F-FDG PET/CT uptake and leucocyte-labeled scintigraphy for the driveline. (**A**) ^{18}F-FDG PET/CT scan showing a linear uptake along the entire driveline, grade B, without extension to soft tissues (3D view, red curved arrow, axial views, white arrows). No uptake was remarkable along the cardiac-LVAD (Heartmate II). (**B**) Leucocyte-labeled scintigraphy found no uptake on the driveline (white arrows) or cardiac-LVAD-device. It was interpreted as negative. This patient (patient #23) presented a serious respiratory infection at the moment of the implantation of the Heartmate II. Bacteriological examination of sputum and hemoculture were positive to *Staphylococcus aureus*. The ^{18}F-FDG PET/CT scan and the leucocyte-labeled scintigraphy were both completed 2 months after the beginning of the antibiotherapy. The patient was classified as non-VAD-related infection, and the ^{18}F-FDG PET/CT scan was considered as false positive.

positive value, and predictive negative values, respectively, of 71.4%, 100%, 100%, and 33.3%.

Leucocyte scintigraphy examination results were positive in 14 patients out of the 21 patients with VAD-specific or VAD-related infection.

Seven patients had false-negative leucocyte scintigraphy results with clinical or bacteriological evidence of infection. A bacteriological proof of infection (positive purulence at the exit site of the DL/positive blood culture/positive culture of LVAD) was found in six patients. One patient presented only a rapidly evolving cutaneous ulcer at the DL exit site with a scab, without any positive bacteriological analysis (patient #13; Table 3). However, he was considered as infected at the DL exit site of the LVAD and received antibiotics after undergoing PET/CT and leucocyte scintigraphy. For the seven false-negative cases, an antibiotherapy was initiated in five patients (patients #10, 15, 16, 17 and 19; Table 3) before nuclear tests.

There were no false-positive cases (leucocyte scintigraphy negative in all three cases of non-VAD-related infection), leading to a specificity of 100%.

Comparison of ^{18}F-FDG PET/CT and Radiolabeled Leucocyte Scintigraphy SPECT Results

The sensitivity of ^{18}F-FDG PET/CT (visual analysis) was significantly higher than leucocyte scintigraphy (P=0.01). Leucocyte scintigraphy had better specificity (100%) than ^{18}F-FDG PET/CT (66.7%) but the difference did not reach significance (P=0.32). There was no significant difference between ^{18}F-FDG PET/CT and leucocyte scintigraphy for the PPV (P=0.31) and NPV (P=0.14).

DISCUSSION

Diagnosis of LVAD infections is sometimes difficult to make, and it is considerably improved by multimodality imaging. Given that LVAD infections are associated to an important morbidity and mortality, it is helpful to rapidly target the good examination in order to avoid noncontributory results. Currently, there is no consensus on the nuclear examination technique to prioritise, or the criteria for interpretation. The main finding of the present study is that ^{18}F-FDG PET/CT

shows better sensitivity than leucocyte scintigraphy for detecting LVAD infections. Both visual and quantitative analyses of ^{18}F-FDG PET/CT allow high diagnostic performance without statistical significant difference and should be combined for optimal image interpretation.

^{18}F-FDG PET/CT

PET/CT has several advantages: its availability, easier protocol and good spatial resolution. It enables imaging all possible sites of infection (pocket/generators, leads) and extracardiac complications at the same time (metastatic infection and septic emboli). Salomäki et al[15] reported that diagnostic performances of ^{18}F-FDG PET/CT are better for the detection of paravalvular infection associated with prosthetic valve endocarditis than with native valve endocarditis. Prosthetic valve endocarditis could cause more abscesses than native valve endocarditis and therefore be more detectable on imaging because of a large amount of inflammatory cells.

No consensus exists concerning the criteria of interpretation for ^{18}F-FDG PET/CT in LVAD infections. Jimenez-Ballvé et al[16] compared different interpretation criteria in prosthetic infective and CIED infections, and the best method appeared to be a visual analysis of PET images both with and without attenuation correction. This method was particularly useful when evaluating the presence of artifacts due to the presence of metal components. They also found a good accuracy of quantitative analysis, with an optimal SUV_{max} threshold of 5.5 (vs 4.5 in our study). However, it is difficult to establish a fixed threshold to discriminate between physiological and pathological uptakes, as there are many factors influencing the uptake. This lack of reliability is increased with the use of different PET cameras.

In another study, Avramovic et al[4] found that the use of the metabolic volume yields very high accuracy in the detection of LVAD DL infections, but this criterion was not explored in our study.

However, ^{18}F-FDG PET/CT also presents some limitations. The most important one is certainly its lack of specificity since increased glucose utilization can be seen in numerous neoplastic, postoperative, inflammatory, and infectious processes. An optimal preparation is also required with a high-fat low-carbon diet, in order to avoid physiological myocardial uptake and potential sources of misinterpretation.

Finally, the timing of ^{18}F-FDG PET/CT remains controversial shortly after surgery,[9] because of FDG uptake in postoperative inflammation. In that context, leucocyte scintigraphy could be more specific than PET/CT and could be considered a better option.

In a meta-analysis, Juneau et al[8] reported high sensitivity (87%) and specificity (94%) of ^{18}F-FDG PET/CT in the diagnosis of CIED infection. We found specificity of 66.7%, but this result was due to the low proportion of non-VAD-related, infected patients (3/24) with one false-positive result, leading to a weak specificity, probably not reflecting reality. In this study, the sensitivity of ^{18}F-FDG PET/CT was 95.2%. It is better than that in Juneau's meta-analysis, but this difference could be due to the fact that they analyzed a different cardiac device (10 studies about CIED infections, one study about LVAD infections exclusively). Dell'Aquila et al[6] performed ^{18}F-FDG PET/CT in 31 patients with LVAD for a suspicion of infection, and found sensitivity of 100% and specificity of 80%, closer to our findings.

Leucocyte Scintigraphy

By targeting the main cells involved in infectious processes, leucocyte scintigraphy is an interesting imaging technique for suspicion of LVAD infections. However, there are some limitations that need to be mentioned. First, radiolabeling of leukocytes involves direct handling of blood products. Second, patients have to come for 2 days straight, and the signal detected with leucocyte scintigraphy is weak on 24 hours post-injection images. Leucocyte scintigraphy is also lengthier than ^{18}F-FDG PET/CT: the examination requires the acquisition of images 30 minutes, and 4-6 and 20-24 hours after injection of the radiotracer. Finally, the spatial resolution and sensitivity are intrinsically lower in single-photon γ cameras than those in PET systems.[17] There are few studies evaluating the diagnostic performance of leucocyte scintigraphy in LVAD infections. Erba et al[10] reported sensitivity of 94% and specificity of 100% in 63 patients for a suspected device-related infection, whereas a small study that enrolled 13 LVAD patients reported sensitivity and specificity of 100%.[9] In this study, we reported sensitivity of 71.4% due to an important number of false negatives of leucocyte scintigraphy (N=7). This could be explained by the initiation of antibiotherapy in five patients in our study, whereas no antibiotherapy was initiated before leucocyte scintigraphy in Erba's study.

Discordant Cases

There were seven discordant cases between PET and leucocyte scintigraphy results. Six patients presented an infection (4 VAD-specific infection and 2 VAD-related infection), with true positive PET results and false-negative SPECT. The proportion of false

negatives with leucocyte scintigraphy was more important for the interpretation of the DL site (N=3) than the cardiac device (N=1).

In total, ^{18}F-FDG PET/CT found more uptake foci on the DL (N=20) than leucocyte scintigraphy (N=12). In most cases of both positive PET/CT and leucocyte scintigraphy for the DL, the FDG uptake was extended to soft tissues nearby (grade C). On the contrary, focal or segmentary uptake on ^{18}F-FDG PET/CT without extension to soft tissue (grade B) was rather associated to negative leucocyte scintigraphy results for the DL. This difference could partly be explained by the lower spatial resolution of leucocyte scintigraphy (<10-15 mm), since septic foci extended along the DL without extension to soft tissue are thin, and therefore harder to visualize. Given the better spatial resolution of ^{18}F-FDG PET/CT relative to scintigraphy, ^{18}F-FDG PET/CT could be more performant to see tiny amount of septic material.

In five patients of the seven discordant cases, nuclear tests were performed days to weeks after treatment initiation, where the acute accumulation of leucocytes is replaced by chronic inflammatory such as lymphocytes and plasma cells.[18] This could have increased the proportion of false negatives of leucocyte scintigraphy. In contrast, ^{18}F-FDG PET/CT showed higher sensitivity but lower specificity since FDG uptake was seen in both inflammatory and infectious process.

One patient had false-positive ^{18}F-FDG PET/CT with true negative leucocyte scintigraphy findings (#patient 23, description in "Results" section). He presented a severe respiratory sepsis to *S. aureus*, with no clinical or biological evidence of LVAD infection. Nuclear tests were realized 63 days after the implantation of a Heartmate II, under antibiotherapy. FDG uptake was seen along the DL, without extension to soft tissues. Given the short delay between surgery and the timing of PET/CT, the uptake could have reflected nonspecific local inflammation.

Limitations

This study has some limitations: its retrospective design, the small number of patients, and the population selection, given that all patients had a clinical suspicion of infection (specific LVAD infection, VAD-related infection, or non-VAD-related infection). This population, however, reflects clinical routine. Half of the patients received antibiotics before nuclear medicine examinations which could have affected the sensitivity of both methods. Finally, the cohort was heterogenous since patients had different types of LVAD (Heartware, Heartmate, Jarvik), with different characteristics which could influence the evolution of the infectious process.

NEW KNOWLEDGE GAINED

^{18}F-FDG PET/CT appears to be more sensitive than leucocyte scintigraphy for the detection of LVAD infections. However, leucocyte scintigraphy presents high specificity. ^{18}F-FDG PET/CT could be proposed as first-line nuclear medicine procedure and completed with leucocyte scintigraphy in equivocal cases.

CONCLUSION

Nuclear imaging appears to be helpful for diagnosing and localizing LVAD infections, and should be part of the diagnostic criteria, to adapt patient management. ^{18}F-FDG PET/CT and radiolabeled leucocyte scintigraphy have high accuracy in the diagnosis of infections in patients carrying ventricular devices, with significantly higher sensitivity for ^{18}F-FDG PET/CT. Given its high sensitivity, and its easier protocol, ^{18}F-FDG PET/CT could be proposed as first-line nuclear medicine procedure. Both visual and quantitative analyses of ^{18}F-FDG PET/CT allow high diagnostic performance and should be combined for optimal image interpretation. The validity of this imaging strategy in patients with suspected infection of VADs will need to be confirmed in a prospective clinical study with a larger number of patients.

Disclosure

The authors declare no conflict of interest.

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