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Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography for improving diagnosis of infection in patients on CF-LVAD: longing for more 'insights'

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Aim Presence and consequent extent of infection in patients on continuous-flow left ventricular assist devices (CF-LVADs) can be challenging with the current diagnostic tools. The present study sought to demonstrate the diagnostic power of 18F-Fluorodeoxyglucose-Positron-Emission Tomography/Computed Tomography (18F-FDG PET/CT) in detecting infection in patients supported with CF-LVAD.

Background The present study sought to demonstrate the diagnostic power of ^{18}F-fluorodeoxyglucose-positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) in detecting infection in patients supported with CF-LVAD.

Methods and results Between July 2009 and April 2016, 61 PET/CT examinations were performed in 47 patients (median age 64.13 years, IQR 18.77) supported with a CF-LVAD. PET/CT assessments were performed qualitatively and quantitatively at three different levels: at the piercing site of driveline (first level), along the intracorporeal course of driveline (second level), and around the device (third level). Final diagnosis of LVAD infection was prospectively performed and was based upon microbiological samples taken at hospital admission, during the surgical revision/transplantation and recurrence of symptoms on long-term follow-up. At last follow-up a total of 40 (65.57%) final diagnoses of LVAD-infection could be ascertained. Matching the final diagnosis with the PET/CT assessments the sensitivity, specificity, and positive and negative predictive value were 90.0, 71.4, 85.71, and 78.94%, respectively. Level sub-analyses of SUV max showed an optimal discriminator power for levels 1 and 2 (AUC of level 1—0.824, $P < 0.001$; AUC of level 2—0.849, $P < 0.001$, respectively). At the third level semi-quantitative analysis showed poor discriminator power (AUC 0.589, $P = 0.33$). Qualitative visual analysis instead indicated a trend toward significance ($P = 0.07$).

Conclusions Quantitative ^{18}F-FDG PET/CT is an optimal diagnostic tool in detecting superficial and deep driveline infections. However, diagnostic accuracy with regard to the diagnosis of pump housing infection is limited. Here, clinical and qualitative PET/CT analyses must be better considered.

Keywords VAD • PET (positron emission tomography) • VAD infections

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Introduction

Treatment of heart failure with new generation devices in combination with more adequate preoperative indications[1–3] and postoperative treatments allows patients to be supported for longer time. Although this trend may partially compensate the ongoing lack of organs available for heart transplantation, longer support times expose patients to a higher rate of long-term complications such as infections. In this context diagnosis and extent of the infection to internal ventricular assist device (VAD)-components can play a crucial role in therapeutic management. Moreover, early recognition of left ventricular assist device (LVAD) infection may potentially result in a more appropriate treatment with a consequent attenuation of its deleterious effects. Recent publications have reported several advantages of ^{18}F-fluorodeoxyglucose-positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) in detecting infection of prosthetic valve or cardiovascular implantable electronic devices.[4,5] In this setting, we adopted the same concept to patients on VAD since July 2009 and we hereby report our extensive experience with PET/CT in a reasonable number of patients.

Patients and methods

This is a single-centre study including 61 ^{18}F-FDG PET/CT examinations performed in 47 patients supported with a continuous-flow left ventricular assist devices (CF-LVAD) [82% men, median age 64.1 years, interquartile range (IQR) 18.8] between July 2009 and April 2016. Median interval time between LVAD implantation and PET/CT examination was 13 months (IQR 21.7). In 86.9% (53 of 61) of the examinations, PET/CT was performed in patients supported with the two most currently used devices Heart Ware (HVAD HeartWare International, Framingham, MA, USA) or HeartMate II (Thoratec Corp., Pleasanton, CA, USA). The baseline characteristics of the patients are displayed in *Table 1*. Three patients underwent VAD implantation elsewhere and have been referred to our centre for evaluation of transplantation.

Clinical data were prospectively collected in two informatics systems. The University of Münster Ethical Committee and Institutional Review Board approved the study, and patient consent was waived. PET/CT was performed once in 38 patients while 9 patients underwent repeated examinations (a total of 23 examinations). In details one patient underwent 4, three patients 3 and five patients 2 PET/CT examinations, respectively.

In 24 cases PET/CT was performed although there were no external signs of infection; however, there were clinical signs of infection including recurrence of bacteraemia (in absence of another identifiable source) and/or elevated infectious parameters with fever of unknown origin. The other 29 cases were suspicious for local signs of infection (along the sternotomy scar or at the driveline exit site). In these cases the examination was performed with the aim of confirming the local infection and to determine the extent of infection to the internal VAD components. Finally six patients without signs of infection underwent eight PET/CT examinations. Main indications for PET/CT in these patients were tumour staging and exclusion of a tumour prior to transplantation listing. In details one patient had a bronchial carcinoma (*Table 2*, patient no. 33) and received a total of 3 PET/CT in order to stage the tumour and plan the radiotherapy. Another patient (*Table 2*, patient no. 34) underwent PET/CT for the staging a cervical cancer. In another three patients (*Table 2*, patient nos. 41, 44, and 47) PET/CT was performed in order (*Table 2*, patient no. 39) to exclude the presence of a tumour prior to transplantation listing and in one in order to exclude the presence of intestinal tumour for unclear signs of anaemia.

Table 1 Patients' characteristics

Baseline characteristics	PET/CT examinations *n* = 61
Age (years) IQR	64.13 (18.77)
Sex (female) *n* (%)	11 (18.03)
Diabetes mellitus *n* (%)	10 (16.39)
Glucose mg/L IQR	101.5 (34.0)
Fasting time hours IQR	12 (4)
HVAD (Heartware) *n* (%)	40 (65.57)
Heartmate II (Thorathec) *n* (%)	13 (21.31)
Incor *n* (%)	6 (9.83)
Ventracor. *n* (%)	2 (3.27)
Mean interval time between VAD implantation and PET/CT (months) IQR	13.02 (5.21)
Mean leucocyte count at the time at hospital admission (tsd./ μL) IQR	10.76 (7.84)
Mean leucocyte count at the time of PET (tsd./μL) IQR	9.84 (5.50)
C-reactive protein level at the time of at hospital admission (mg/dL). IQR	5.70 (13.63)
C-reactive protein level at the time of PET (mg/dL). IQR	5.80 (12.40)
Isolated + Swabs *n* (%)	14 (22.95)
Isolated + Blood culture *n* (%)	17 (27.86)
+Swabs + Blood cultures *n* (%)	11 (18.03)
-Cultures *n* (%)	19 (31.15)
Indications	
Local signs of percutaneous site infection *n* (%)	16 (26.26)
Recurrence of bacteraemia in absence of another identifiable source *n* (%)	15 (24.59)
Elevated infect parameters and fever unknown origin *n* (%)	9 (14.75)
Pretransplant evaluation *n* (%)	3 (4.92)
Local infection adjacent the driveline and/or to the lower sternotomy scar suspicious of driveline pocket involvement *n* (%)	4 (6.56)
Evaluation of the antibiotic treatment. *n* (%)	6 (9.84)
Tumour staging *n* (%)	4 (6.56)
Suspect of tumour (unclear signs of anaemia) *n* (%)	1 (1.64)
New local infection adjacent the driveline and to the lower sternotomy scar suspicious of driveline pocket involvement *n* (%)	1 (1.64)
New local signs of percutaneous site infection *n* (%)	2 (3.28)

IQR, interquartile range; AB, antibiotic.

Table 2 Individual results including indications, bacteriological samples, end diagnosis and PET/CT findings

Patient number	Time interval between LVAD and PET/CT (months)	Indication to PET/CT	Blood cultures	Swabs	PET results	Final diagnosis
1	40.5	Elevated infect parameters and fever unknown origin			FP	No device infection
	41.8	New local signs of percutaneous site infection	*Enterobacter aerogenes*/*Staphylococcus epidermidis*		TP	Driveline Infection
	43.1	Evaluation of the antibiotic treatment	*Propionibacterium acnes*/*Enterobacter aerogenes*		TP	Driveline infection
2	19.4	Recurrence of bacteraemia in absence of another identifiable source	MRSA (methicillin-resistant *Staphylococcus aureus*)		TP	Driveline infection
	22.6	Recurrence of bacteraemia in absence of another identifiable source	MRSA (methicillin-resistant *Staphylococcus aureus*)		TP	Driveline infection
3	14.5	Elevated infect parameters and fever unknown origin			TN	No device infection + Colon pathological uptake[a]
4	1.0	Recurrence of bacteraemia in absence of another identifiable source	*Enterococcus faecalis*		TN	No device infection
5	5.9	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		FN	Device infection
6	1.2	Elevated infect parameters and fever unknown origin			TN	No device infection
7	0.4	Elevated infect parameters and fever unknown origin			TN	No device infection
8	0.6	Recurrence of bacteraemia in absence of another identifiable source	*Streptococcus* sp./*Propionibacterium acnes*		TN	No device infection + pneumonia
9	5.7	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		TP	Driveline infection and device infection
	8.9	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		TP	Driveline infection + paravertebral abscess
	13.0	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*	*Proteus mirabilis*	TP	Driveline infection + Colon pathological uptake[a]
	14.1	Evaluation of the antibiotic treatment	*Staphylococcus aureus*	*Proteus mirabilis*	TP	Driveline infection and device infection
10	4.4	Recurrence of bacteraemia in absence of another identifiable source	*Candida albicans*		TN	No device infection + pulmonary abscess
11	13.0	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		TP	Driveline infection

Continued

Table 2 *Continued*

Patient number	Time interval between LVAD and PET/CT (months)	Indication to PET/CT	Blood cultures	Swabs	PET results	Final diagnosis
12	0.8	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		TP	Driveline infection and device infection
	2.7	• New local infection adjacent the driveline and to the lower sternotomy • Scar suspicious of driveline pocket involvement	*Staphylococcus aureus*	*Staphylococcus aureus*	TP	Driveline infection and device infection
13	12.2	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus epidermidis*		TP	Driveline infection + colon pathological uptake[a]
14	14.1	Elevated infect parameters and fever unknown origin			FP	No device infection + pace maker infection
15	13.2	Local signs of percutaneous site infection		*Staphylococcus aureus*	TP	Driveline infection
16	32.3	Local signs of percutaneous site infection		*Enterococcus faecalis*	TP	driveline infection
17	27.5	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		TP	Driveline infection
	26.1	New local signs of percutaneous site infection	*Staphylococcus epidermidis*	*Staphylococcus aureus*	TP	Driveline infection
18	20.2	Local signs of percutaneous site infection	*Proteus mirabilis*	*Proteus mirabilis*	TP	Driveline infection and device infection
19	1.7	Local signs of percutaneous site infection			TP	Driveline infection
20	16.9	Local signs of percutaneous site infection		*Staphylococcus capitis*	TP	Driveline infection
21	8.9	Local signs of percutaneous site infection	*Staphylococcus aureus*		FN	Device infection
22	10.2	Local signs of percutaneous site infection		*Serratia marcecens/ Hämophilus influenzae*	TP	Driveline infection and device infection
	9.4	Evaluation of the antibiotic treatment		*Serratia mecescens/ Haemophilus influenzae/Haemophilus parainfluenzae*	TP	Driveline infection and device infection
23	2.5	Local signs of percutaneous site infection	*Staphylococcus aureus*	*Staphylococcus aureus*	TP	Driveline infection and device infection
24	7.6	Local signs of percutaneous site infection		*Klebsiella oxytoca/ Pseudomonas aeruginosa*	TP	Driveline infection
25	5.2	• Local infection adjacent the driveline and to the lower sternotomy		*Staphylococcus epidermidis*	FN	Driveline infection

Continued

Table 2 *Continued*

Patient number	Time interval between LVAD and PET/CT (months)	Indication to PET/CT	Blood cultures	Swabs	PET results	Final diagnosis
		• Scar suspicious of driveline pocket involvement				
	48.3	Evaluation of the antibiotic treatment	*Staphylococcus hominis*	*Staphylococcus epidermidis*	TP	Driveline infection and device infection
	50.1	Evaluation of the antibiotic treatment		*Staphylococcus epidermidis*	TP	Driveline infection
26	11.1	Local signs of percutaneous site infection			TP	Driveline infection
27	4.2	• Local infection adjacent to the lower sternotomy • Scar suspicious of driveline pocket involvement		*Streptococcus mitis/ oralis*	TP	Device infection
28	20.4	Local signs of percutaneous site infection	MRSA (methicillin-resistant *Staphylococcus aureus*)	*Staphylococcus epidermidis /haemolyticus*	TP	Driveline infection
29	0.7	Local signs of percutaneous site infection	*Staphylococcus aureus*	*Staphylococcus aureus*	TP	Driveline infection and device infection
30	7.3	Local signs of percutaneous site infection	*Staphylococcus aureus*	*Staphylococcus aureus*	TP	Driveline infection
	12.6	Evaluation of the antibiotic treatment	*Staphylococcus aureus*	*Staphylococcus aureus*	TP	driveline infection
31	6.1	• Local infection adjacent the driveline and to the lower sternotomy • Scar suspicious of driveline pocket involvement		*Enterobacter cloacae* complex	TP	Driveline infection and device infection
32	0.3	Recurrence of bacteraemia in absence of another identifiable source	*Serratia marcescens*		TN	No device infection
33	26.0	Staging of lung cancer			TN	No device infection
	29.4	Staging of lung cancer			FP	No device infection
	31.0	Staging of a Staging of lung cancer carcinoma			TN	No device infection
34	25.6	Staging of cervical cancer			TN	No device infection
35	3.9	Elevated infect parameters and fever unknown origin			FP	No device infection + pneumonia
36	5.2	Elevated infect parameters and Fever unknown origin			FP	pneumonia + Colon pathological uptake[a]
37	15.1	Local signs of percutaneous site infection		*Staphylococcus aureus*	TP	Driveline infection
38	31.0	Recurrence of bacteraemia in absence of another identifiable source	*Staphylococcus aureus*		FN	Pneumonia + outflow graft infection
39	9.2	Suspect of tumour (unclear signs of anaemia)			TN	No device infection

Continued

Table 2 *Continued*

Patient number	Time interval between LVAD and PET/CT (months)	Indication to PET/CT	Blood cultures	Swabs	PET results	Final diagnosis
40	27.0	• Local infection adjacent the driveline and to the lower sternotomy • Scar suspicious of driveline pocket involvement		*Staphylococcus aureus*	TP	Driveline infection
41	22.5	Pretransplant evaluation			FP	No device infection
42	30.6	Local signs of percutaneous site infection		*Staphylococcus aureus*	TP	Driveline infection
43	8.7	Local signs of percutaneous site infection		*Staphylococcus aureus*	TP	Driveline infection
44	3.6	Pretransplant evaluation			TN	No device infection
45	49.5	Elevated infect parameters and fever unknown origin			TN	No device infection Colon pathological uptake[a]
46	29.4	Elevated infect parameters and fever unknown origin			TN	No device infection + pneumonia
47	32.5	Pretransplant evaluation			TN	No device infection

[a]PET/CT showed in those patients a Colon pathological uptake, colonoscopy or/and histopathology showed later in patient nos. 3 and 9 diverticultis, in patient nos. 13 and 36 colon adenoma and angiodysplasia in patient no. 45.

Table 2 reports in details all indications. Regarding the indication to PET/CT the attending surgeon and cardiologist responsible of LVAD program were involved in all cases. Final diagnosis (standard of reference) of LVAD specific infection was prospectively performed based upon microbiological samples taken at hospital admission, during the surgical revision/transplantation and recurrence of symptoms on long-term follow-up. Infection was defined according to the adverse event definition of the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS). This includes a positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body unless strong clinical evidence despite negative cultures, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.[6] Positron-emission tomography/computed tomography findings have only been regarded as additional/contributive information and were never the sole determinant for the final patient management decision. Consequently, diagnostic procedures following PET/CT assisted the physicians to confirm or dismiss the clinical relevance of PET/CT findings.

Patient preparation and PET/CT examination

Details concerning the ^{18}F-FDG PET/CT procedures have been published elsewhere.[7,8] To optimally suppress glucose uptake in the myocardium, all patients were studied after fasting for at least 6 h. In details the lowest interval was 8 h and the median fasting hour was 12 h (IQR 4 h). Blood glucose levels at the time of ^{18}F-FDG application were less than 185 mg/dL. A body-weight-adapted activity of ^{18}F-FDG (5 MBq/kg of body weight) was injected intravenously approximately 60 min before PET data acquisition (mean activity: 344 ± 10.84 MBq, range 226–545 MBq). The scans were obtained using a hybrid PET/CT system [Biograph Sensation 16; Siemens Medical Solutions (n = 43) or Siemens Biograph m CT; Siemens Medical Solutions (n = 18)]. Low-dose CT of the entire area covered by PET (from skull base to the mid-thigh level) was performed for attenuation correction and anatomical correlation in all patients. After completion of the CT scan, PET data were acquired for 3 min per bed position. Positron-emission tomography images were reconstructed using the standard manufacturer-supplied software.

PET image analysis and statistical analysis

All PET/CT scans were reviewed and analysed by two readers, experienced in PET analysis, who were not aware of clinical signs and symptoms, or of the final diagnosis. Image analysis was performed using the Siemens Syngo.via software (Version 2). ^{18}F-FDG uptake was measured using the function volume-of-interest (VOI). The VOIs were approximately the same size (30 cm^3). Special care was taken in excluding spill-over from neighbouring organs or ^{18}F-FDG avid structures. ^{18}F-FDG uptake was evaluated both, qualitatively and quantitatively at the driveline skin penetration point (level 1) and along the driveline subcutaneously (level 2) in the attenuation-corrected PET images, as well as qualitatively and semi-quantitatively around the LVAD aggregate (level 3) in the uncorrected PET images. Analysis of attenuation corrected images at this level was intentionally not performed due to strong attenuation artefacts predominately present in the area. In fact metallic implants generate artefacts on CT images because of their high photon absorption.[9] This increase in Hounsfield units results in correspondingly high PET attenuation coefficients,

which lead to an overestimation of tracer concentration in that region and thereby could result in a false-positive PET finding. Qualitative analysis of uncorrected PET images was performed by a visual grading system using a 4-point scoring system (0: none 1: slightly elevated but lower then lung uptake, 2: moderate uptake, but less or equal as liver uptake, 4: uptake levels higher then liver uptake). Thereafter, visual scores were compared with the report of the nuclear medicine physician at the time of the exam. For quantitative analysis SUV max and SUV mean were considered. A semi-quantitative analysis of the uncorrected PET series was performed using target-to-background ratios (TBR) between absolute maximum counts in the VOI around the LVAD aggregate and absolute mean counts in a VOI in the right deltoid muscle and the right lung lobe with no signs of pathological processes. Data are presented as median (IQR) for continuous variables and categorical variables are expressed as frequencies. Comparisons of PET assessments for each level between patients with and without VAD infection were performed using the Mann–Whitney *U*-test. A receiver operating characteristic (ROC) curve was calculated from the SUV max regarding the first level (driveline) and for the semi-quantitative TBR regarding the third level (pump housing). This allowed assessing the cut-off values with the combination of the best sensitivity and specificity to detect infection (presence = 1; absence of infection = 0). Statistical significance was assumed at a value of $P < 0.05$. Data analysis was performed using SPSS for Windows (Version 23/SPSS Inc., Chicago, IL, USA) and Excel 2010 (Microsoft, Redmond, WA, USA).

Final diagnosis and management

After a median time interval of 4.36 months (lower quartile = 2.89, upper quartile = 8.75) between PET/CT and last follow-up in July 2016 a total of 40 (65.6%) LVAD infections were ascertained. Cultures and procedures that lead to the final diagnosis of infection included as follows: blood cultures were positive in 13 cases, isolated positive swabs cultures at the exit site of driveline in 12, in 13 cases there were a positive blood culture and swabs. In two patients despite recurrence of symptoms microbiological cultures remained negative. A total of 29, 37 and 13 of superficial, deep driveline and pump housing infections could be ascertained at last follow-up. A total of 19 patients underwent urgent heart transplantation whereas 15 patients were still alive on VAD at last follow-up, of them 31 surgical driveline revisions were necessary in 5 patients. One patient underwent LVAD removal due to heart recovery and 12 patients died while on VAD.

PET findings

Abnormal tracer uptake suggestive of infection of the LVAD components was found in 42 (68.85%) examinations. Matching with the final diagnosis there were 36 true positive, 15 true negative, 4 false negative, and 6 false positive findings resulting in an overall sensitivity, specificity, and positive and negative predictive value of 90.0, 71.4, 85.7, and 78.9%, respectively. *Figures 1–3* show two true positive and one true negative findings, respectively. Four patients with normal PET/CT findings had a

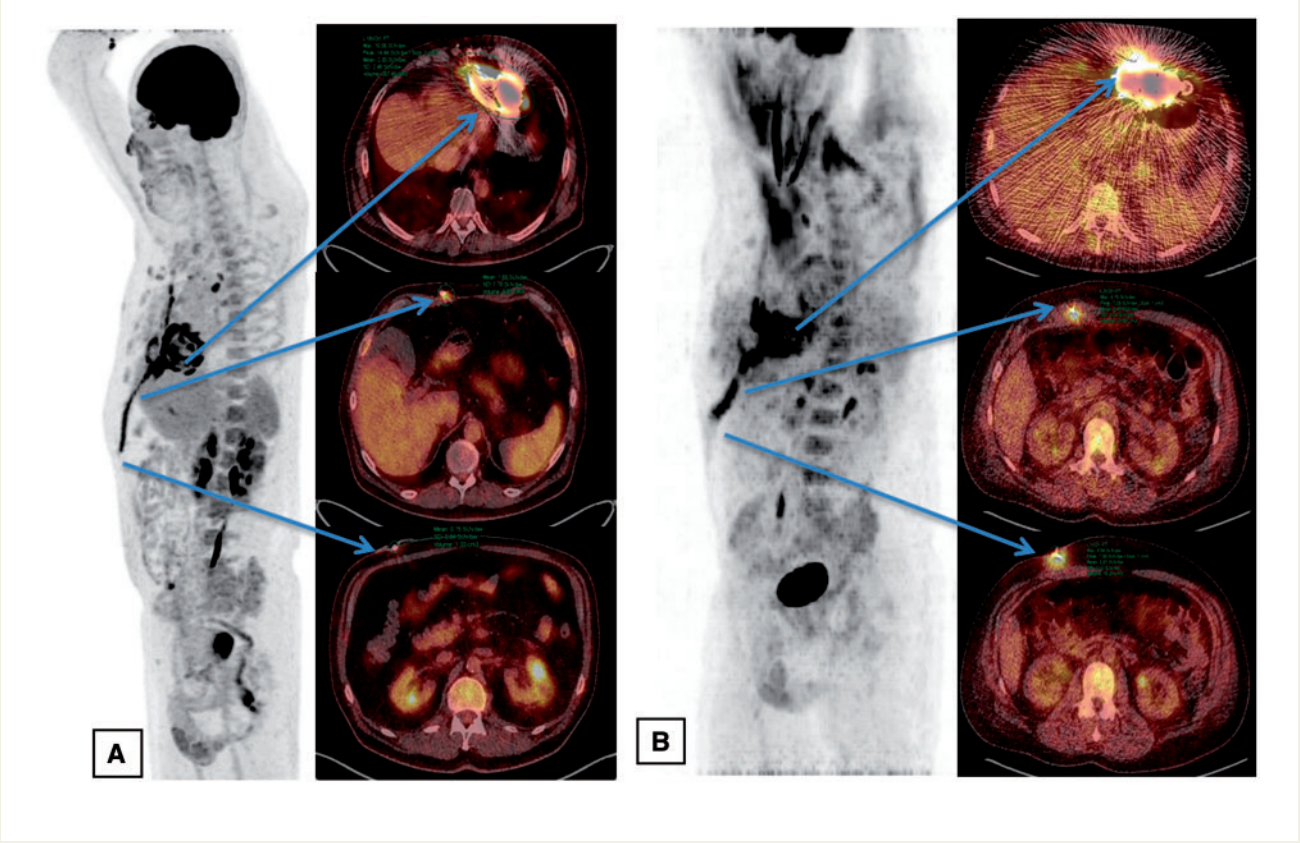

Figure 1 Maximum intensity projections and fused transaxial PET/CT images. (A) pathological ^{18}F-FDG accumulation located at second and third level (arrows). (B) pathological ^{18}F-FDG accumulation located at all levels (arrows).

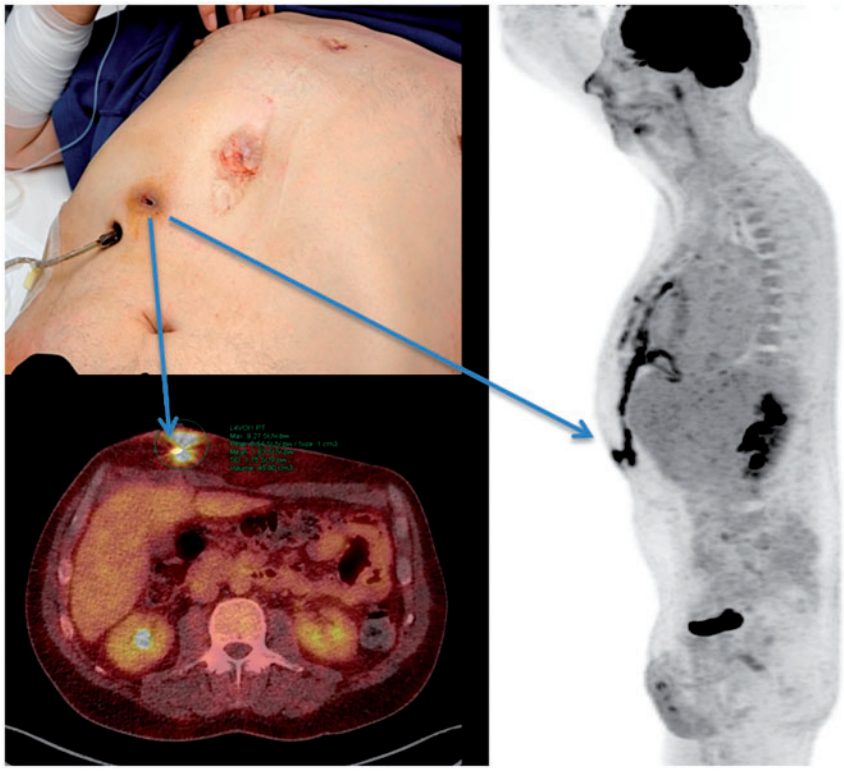

Figure 2 Lateral view of positron emission tomography scan (right) in comparison to external clinical aspect (picture on the left) (patient no. 25). The arrows show pathological ^{18}F-FDG accumulation located in correspondence of the fistula (arrows)

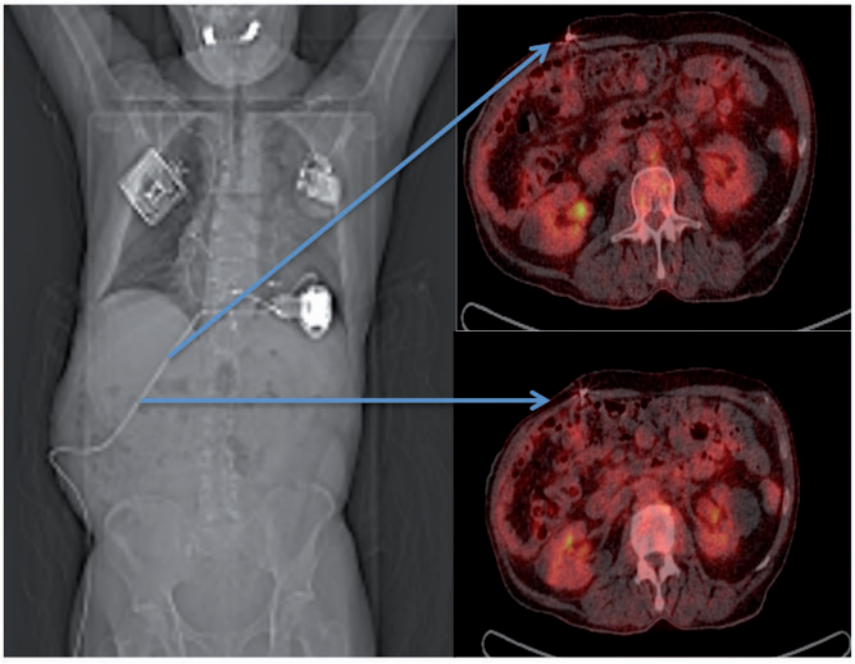

Figure 3 Frontal view of CT scan: normal ^{18}F-FDG uptake of superficial and deep driveline (true negative finding, patient no. 33).

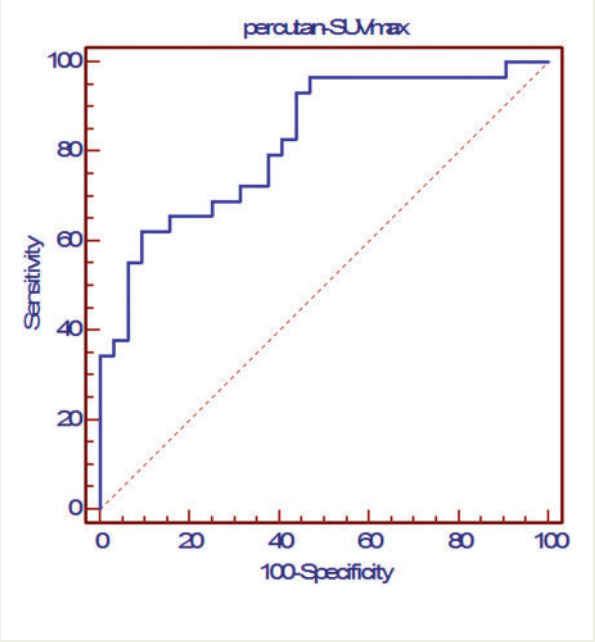

Figure 4 Receiver-operating characteristic curve of maximum standardized uptake value (SUV max) for the diagnosis of superficial driveline infection.

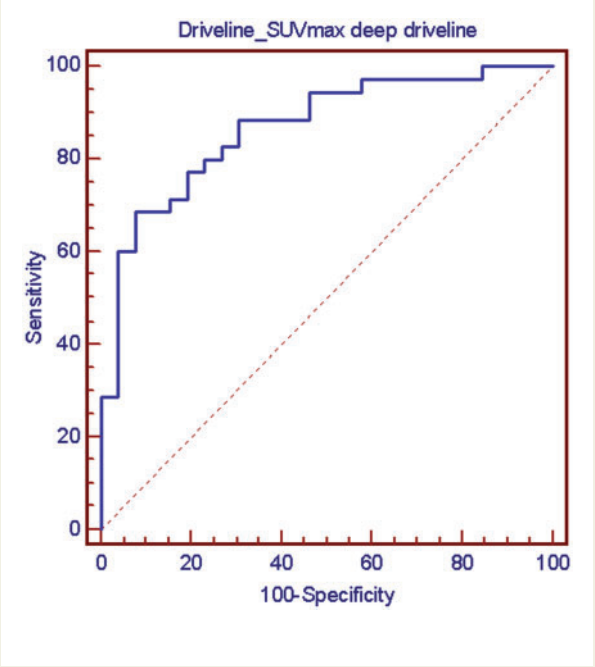

Figure 5 Receiver-operating characteristic curve of maximum standardized uptake value (SUV max) for the diagnosis of deep driveline infection.

LVAD infection (false negative). Three of them had a blood stream infection. Of them in one (*Table 2*, patient no. 38) ^{18}F-FDG uptake could be detected along the outflow graft (Dacron graft) of VAD connected to the aorta which was classified as a non-VAD infection. This patient was successfully treated with antibiotics and any relapse could be recorded. In another patient (patient no. 21) during the transplantation occurred 44 days after the PET/CT a pericardial sterile fluid collection could be observed as signs of past LVAD infection. In this case, the long antibiotic treatment could explain the false negative findings. Another patient (patient no. 5) with positive blood cultures without other possible focus of infection died from an intracranial haemorrhage. In this case we cannot exclude the possible infection of inner surface of LVAD that generated septic emboli. Hence in this case the false negative can be due to the bad performance of PET/CT in the diagnosis of pump housing infection. In the last patient (patient no. 25), the presence a chronic fistula could have been the cause for the low performance of the PET. Six patients with an abnormal ^{18}F-FDG uptake of VAD components did not have any VAD-Infection (false positive). Interestingly, one of them (patient no. 1), despite a positive PET/CT finding and no signs of LVAD infection (negative swabs und negative blood cultures), underwent a second PET/CT examination 1 month later that confirmed clinical signs of infection (positive blood culture). One patient (patient no. 33) who underwent PET/CT for evaluation for transplantation and one for tumour staging had a positive PET/CT finding at the driveline skin penetration point, however all microbiological samples remained negative. Eleven cases among the 57 examinations performed for suspected LVAD infection showed non-VAD-related findings suspicious for infection including the following localizations: lung (five cases), intestines (five cases), spinal cord (one case), and cardiovascular implantable electronic device infections (two cases). Ten patients (patient nos. 4, 6, 7, 8, 12, 12, 19, 23, 29, and 32) underwent PET/CT within 3 months after the LVAD implantation. Five patients were true positive and five true negative. Neither false positive nor negative findings were reported. Four of five patients with a true positive finding underwent heart transplantation after a median of 1.74 month (lower quartile = 0.75, upper quartile = 3.77). During the transplantation in three patients pus collection could be detected around the pump housing. In another patient, surgical samples revealed *Staphylococcus aureus*. Another patient underwent surgical revision and VAC treatment of the driveline. In three of the true negative patients PET/CT detected another focus responsible for the infection, including pneumonia in one and leg abscess in two patients.

Level sub-analysis

A total number of 29 superficial and 35 deep driveline infections could be recorded at the last follow-up. Regarding the superficial infection (first level) sub-analysis of SUV max showed an optimal discriminator power (AUC of level 1—0.824 95% CI 0.706–0.910, $P < 0.001$). A SUV max cut-off value of ≥5.95 led to 62.1% sensitivity and 90.6% specificity (*Figure 4*). Patients with a superficial driveline infection had a median SUV max at the driveline skin penetration point of 6.62 compared with patients without superficial driveline infection, median SUV max 2.15 ($P < 0.001$). Qualitative analysis indicated a median visual score of 3 (lower quartile = 2, upper quartile = 3) for patients with percutaneous infection vs. 0.5 (lower quartile = 0, upper quartile = 2) in patients without ($P < 0.001$). Regarding the second level sub-analyses of SUV max confirmed an optimal discriminator power for levels (AUC of level 2—0.849, CI 0.734–0.928, $P < 0.001$). A SUV max cut-off value of 3.93 led to 80.0% sensitivity and 76.9% specificity (*Figure 5*). Patients with a deep driveline infection had a median SUV max of 8.83 vs. 2.97

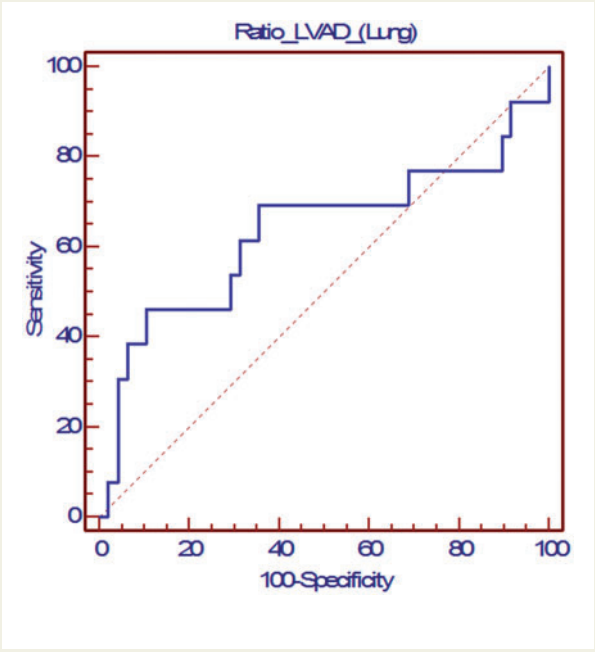

Figure 6 Receiver-operating characteristic curve for semi-quantitative ratio (lung) at the third level (pump housing).

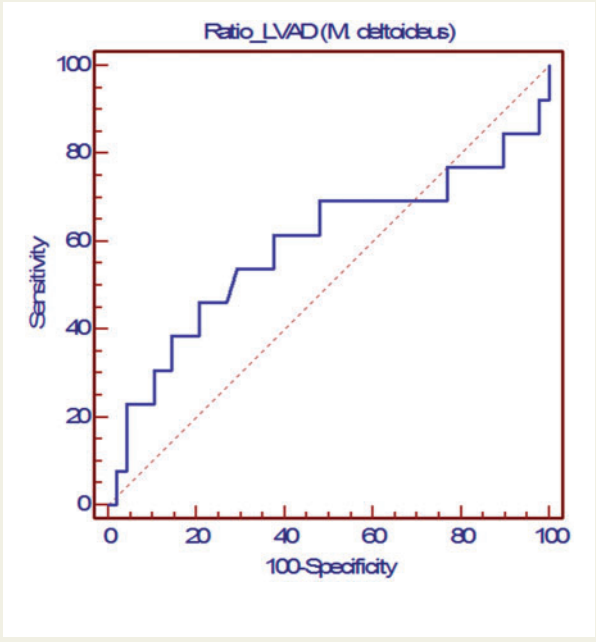

Figure 7 Receiver-operating characteristic curve of semi-quantitative ratio (right deltoid muscle) at the third level (pump housing).

in patients without deep driveline infection ($P < 0.001$). Qualitative analysis indicated a median visual score of 3 (lower quartile = 3, upper quartile = 3) for patients with deep driveline infection vs. 1 (lower quartile = 1, upper quartile = 1) in patients without ($P < 0.001$).

At the third level (pump housing) semi-quantitative analysis showed poor discriminator power (AUC 0.589, 95% CI 0.456–0.713, $P = 0.33$). Patients with a pump housing infection had a TBR to lung parenchyma of 2.26 vs. 1.43 in patients with and without ($P = 0.144$) and a TBR to deltoid muscle of 2.80 vs. 2.07 ($P = 0.32$) (*Figures 6 and 7*), respectively. Moreover qualitative analysis indicated a median visual score of 3 (lower quartile = 0, upper quartile = 3) for patients with pump infection vs. 0 (lower quartile = 0, upper quartile = 3) in patients without pump infection ($P = 0.07$). All PET/CT assessments and the different comparisons between patients with and without VAD infection according to the different levels are presented in *Table 3*.

Patients without signs of infection (eight PET/CT examinations) had the following values: the median SUV max at piercing site of driveline was 2.18 (2.54 IQR) and along the intracorporeal course of the driveline 3.23 (IQR 1.8), respectively. For the pump housing the TBR to deltoid muscle was 1.65 (IQR 0.98) and the TBR to lung parenchyma was 1.05 (IQR 1.47).

Discussion

The current study is the first report in literature dealing with a reasonable number of ^{18}F-FDG PET/CT examinations performed in patients supported with a CF-LVAD. The main finding emerging from it is the high diagnostic power of PET/CT in detecting driveline infections. The hereby reported sensitivity and specificity for VAD infection were 90%, 71.4% with a positive and negative predictive value of 85.7 and 78.9%, respectively. Moreover, PET/CT not only enables the physician to detect driveline infection, but can also reveal other non-VAD-related infection foci. All these findings represented a solid basis for a potentially better treatment of our patients.

In the near future, due to the organ shortage for heart transplantation and due to longer life expectancy with consecutively age-related heart disease, physicians involved in the treatment of heart failure will face an exponential growing number of patients on LVAD. This growth will likely be exacerbated by better survival rates due to new devices, improved preoperative indications for VAD implantation and the postoperative management. As consequence we will face a growing number of patients with LVAD presenting long-term complications such as infection. In this setting, several groups have already shown the deleterious effects of infection in patients on VAD.

To date, John *et al.*[10] reported among a cohort of 332 patients supported with a HVAD a driveline infection rate of 0.25 events per patient-year. Statistical analysis showed no negative impact on survival in patients with driveline exit-site infections, however there was a trend toward reduced survival in patients with sepsis events when compared to those without.

Dealing with a larger cohort (2006 CF-LVAD recipients), Goldstein *et al.*[11] found after a mean follow-up of 8.1 months significantly ($P < 0.01$) better survival in patients without percutaneous driveline infection.

Gordon *et al.*[12] showed in a prospective, multicentre study (11 US cardiac centres, 150 patients) in patients supported with Heartmate that VAD infection significantly increases 1-year mortality (HR = 5.6; $P < 0.0001$).

Koval *et al.*[13] found after median period of 232 days (longer than the abovementioned studies) an increased risk for death in patients with driveline infection while on VAD support (HR 2.20, $P = 0.01$).

Table 3 Differences in the PET/CT assessments between patients with and without level infection

		Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	Median	Lower quartile	Upper quartile	*P*
		Total = 61			No infection = 32			Infection = 29			
Level 1	Visual score	2.00	0.00	3.00	0.5	0	2	3	2	3	<0.001
	SUVmax	4.15	1.89	7.07	2.155	1.69	4.87	6.62	3.69	9.8	<0.001
	SUVpeak	2.99	1.42	5.47	1.61	1.18	3.33	5.16	2.75	6.79	<0.001
	SUVmean	0.88	0.57	1.50	0.70	0.52	1.05	1.46	0.88	2.04	<0.001
				No infection = 26			Infection = 35				
Level 2	Visual score	3.00	1.00	3.00	1	1	1	3	3	3	<0.001
	SUVmax	5.29	2.97	9.26	2.97	2.07	3.90	8.83	4.96	12.65	<0.001
	SUVpeak	3.44	2.06	7.39	2.09	1.52	2.58	6.54	3.68	9.65	<0.001
	SUVmean	1.35	0.90	3.14	0.91	0.63	1.12	3.08	1.72	3.53	<0.001
				No infection = 48			Infection = 13				
Level 3	Visual score	0.00	0.00	3.00	0.00	0.00	3.00	3.00	0.00	3.00	0.077
	Ratio LVAD (deltoid muscle)	2.25	0.97	3.37	2.07	1.12	3.20	2.80	0.85	5.17	0.324
	Ratio LVAD (Lung)	1.48	0.60	2.86	1.43	0.60	2.06	2.26	0.73	3.73	0.144

In this context it is out of debate that early diagnosis of infection can provide the basis for a prompt management of these patients potentially resulting in an attenuation of the deleterious effects of infection. Literature has already shown that there have been attempts to detect infection through ^{18}F-FDG PET/CT.

To date, Tlili *et al.*[14] reported a case of a 59-year-old female patient with a Haertmate II device who underwent PET/CT because the suspect of assuming deep driveline infection. In the same line, Fujino *et al.*[15] reported a case of 41-year-old man with Dura Heart who underwent PET/CT because of LVAD infection. Kim *et al.*[16] reported a series of five (four VAD infections, one control) patients who underwent PET/CT after LVAD implantation. In this series PET/CT clearly showed the high diagnostic power in detecting driveline infection. In our larger cohort we confirm these findings emphasizing the diagnostic power of PET/CT. A total number of 29 superficial and 37 deep driveline infections could be recorded at the last follow-up. Sub-analyses of SUV max showed an optimal discriminator power for superficial and deep infection. Qualitative analysis showed highly significant differences between patients with and without driveline infection ($P < 0.001$). Despite the optimal discriminator power for both superficial and deep infections there were still some performance differences. The sensitivity of PET/CT for diagnosis of superficial infection was lower comparing with the sensibility regarding the diagnosis of deep driveline infections (62.1 vs. 80.0%). A possible explanation could reside in the local treatment of superficial infections attenuating the signs of infection in PET/CT. In contrast with this finding, the higher sensitivity in diagnosis of deep driveline infection can translate from a clinical point of view into a better understanding of infection extend, potentially enhancing improving the treatment of all foci.

However, the high diagnostic power of PET/CT in detecting driveline infection could not be confirmed for pump housing infections. However qualitative visual analysis indicated a trend towards significance ($P = 0.07$). This limitation is most probably caused by unspecific ^{18}F-FDG uptake due to foreign body reaction around the LVAD on the one hand and physiological tracer uptake into adjacent left ventricular myocardium on the other hand. In our study particular techniques for the suppression of myocardial glucose metabolism such as preparation with low carb diets or administration of heparin were not performed routinely. In further prospective studies dealing with the topic of ^{18}F FDG PET/CT imaging of VAD infections this should optionally be considered. Along with this limitation other possible ones that could have generated the false negative findings might lay in the use of antibiotics prior to PET/CT, the presence of chronic fistula and possible infection of the inner surface of pump housing. The latter can ultimately cause thromboembolic events miming the presence of an endocarditis. At this level (pump housing) despite the non-attenuation corrected imaging the diagnostic power of PET/CT regarding infection of the inner surface of the device remains very limited. Another finding emerging from the present study concerns the timing of PET/CT. Ten patients underwent PET/CT within 3 months after the LVAD implantation. Surprisingly, neither false positive nor negative findings were reported. The high sensitivity could be explained by the high grade of infection that justified the urgent transplantation in these single cases. In fact during the transplantation in three patients pus collection could be observed around the pump housing. Normally, unspecific ^{18}F FDG uptake due to post-implantation changes and post-surgical wound healing is expected in the first weeks to months after surgery so that particularly specificity is limited and false positive results may be observed. In this context, regarding the observed high specificity we believe that only more numerous observations can help draw more solid conclusions and generate better insights. Thus, we advocate caution when interpreting these results obtained early after LVAD implantation.

Further limitations include the retrospective design of study with its disadvantages by nature. PET/CT assessment was not corrected in accordance to the EANM Research Ltd (EARL) criteria. Furthermore a dual time point imaging was not performed and its diagnostic validity must be explored in further prospective evaluations. Moreover

although standard definition of LVAD infection was adopted according to the INTERMACS adverse event definition of Percutaneous Site and/or Pocket Infection, many physicians were involved in the care of LVAD patients and due to the retrospective nature of the study we cannot exclude the presence of possible biases.

Conclusions

^{18}F-FDG PET/CT is a useful imaging modality with a high diagnostic power for the diagnosis and detection of the extent of LVAD related infections. The diagnostic accuracy is highest around the driveline and particularly at the subcutaneous portion. However, the diagnostic power in detecting pump housing infection is limited and requires further investigations.

Conflict of interest: M. Scherer: Consultant/Advisory Board, Thoratec Corporation. All other authors do not have any conflict of interest.

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