

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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Received 26 January 2017; editorial decision 18 May 2017; accepted 24 May 2017; online publish-ahead-of-print 12 July 2017

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 ¹⁸F-fluorodeoxyglucose-positron-emission tomography/computed tomography (¹⁸F-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 ¹⁸F-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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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	<i>Staphylococcus aureus</i>		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	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	TP	Driveline infection and device infection
13	12.2	Recurrence of bacteraemia in absence of another identifiable source	<i>Staphylococcus epidermidis</i>		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		<i>Staphylococcus aureus</i>	TP	Driveline infection
16	32.3	Local signs of percutaneous site infection		<i>Enterococcus faecalis</i>	TP	driveline infection
17	27.5	Recurrence of bacteraemia in absence of another identifiable source	<i>Staphylococcus aureus</i>		TP	Driveline infection
	26.1	New local signs of percutaneous site infection	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus aureus</i>	TP	Driveline infection
18	20.2	Local signs of percutaneous site infection	<i>Proteus mirabilis</i>	<i>Proteus mirabilis</i>	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		<i>Staphylococcus capitis</i>	TP	Driveline infection
21	8.9	Local signs of percutaneous site infection	<i>Staphylococcus aureus</i>		FN	Device infection
22	10.2	Local signs of percutaneous site infection		<i>Serratia marcescens/Haemophilus influenzae</i>	TP	Driveline infection and device infection
	9.4	Evaluation of the antibiotic treatment		<i>Serratia marcescens/Haemophilus influenzae/parainfluenzae</i>	TP	Driveline infection and device infection
23	2.5	Local signs of percutaneous site infection	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	TP	Driveline infection and device infection
24	7.6	Local signs of percutaneous site infection		<i>Klebsiella oxytoca/Pseudomonas aeruginosa</i>	TP	Driveline infection
25	5.2	• Local infection adjacent the driveline and to the lower sternotomy		<i>Staphylococcus epidermidis</i>	FN	Driveline infection

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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 than lung uptake, 2: moderate uptake, but less or equal as liver uptake, 4: uptake levels higher than 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

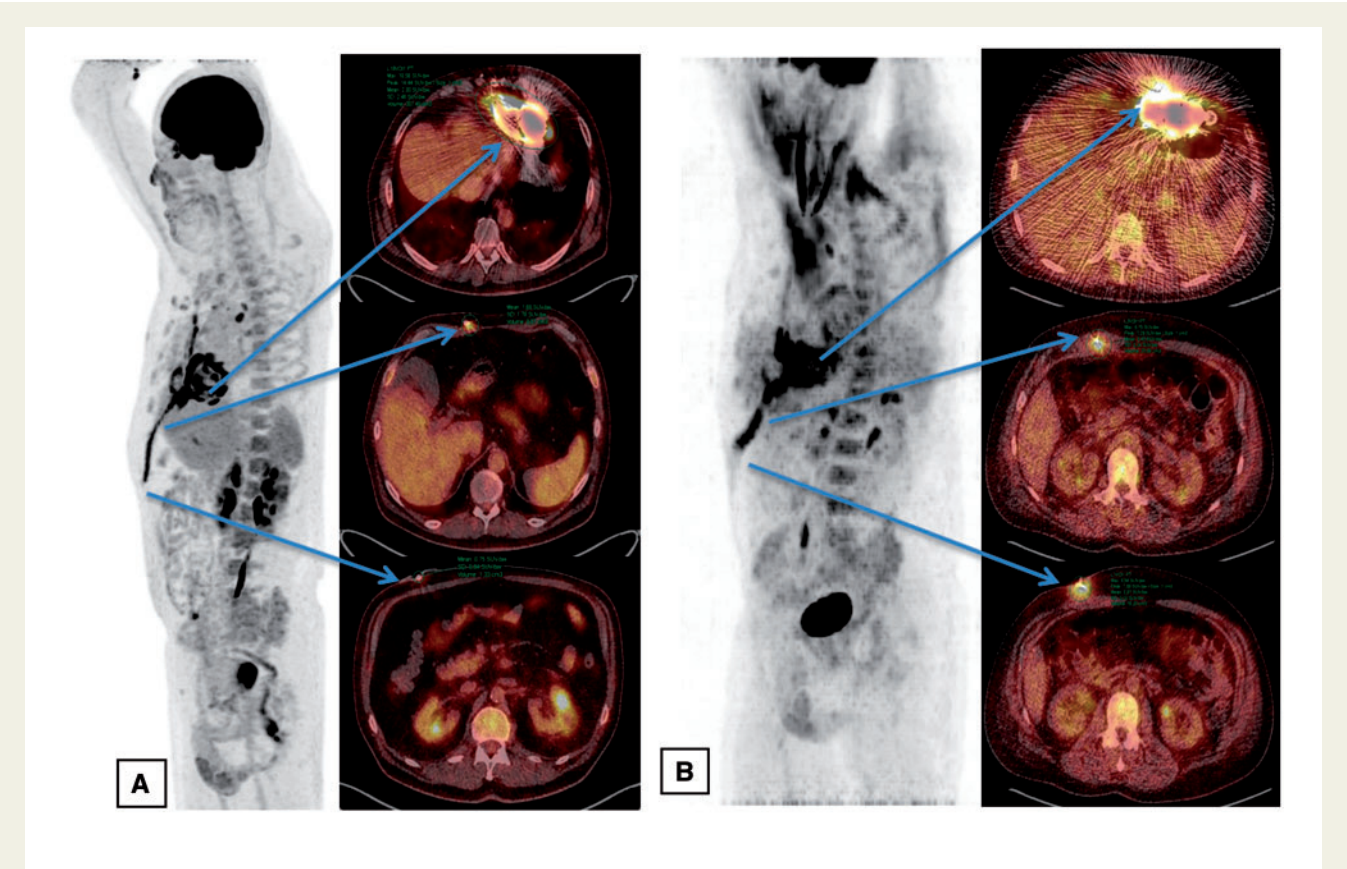


Figure 1 Maximum intensity projections and fused transaxial PET/CT images. (A) pathological ¹⁸F-FDG accumulation located at second and third level (arrows). (B) pathological ¹⁸F-FDG accumulation located at all levels (arrows).

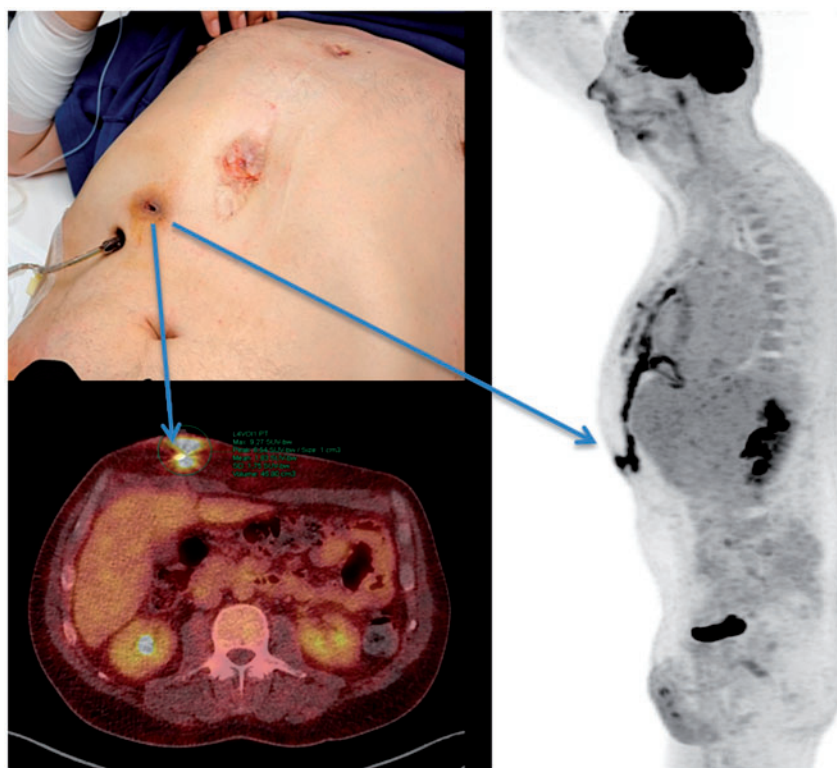


Figure 2 Lateral view of positron emission tomography scan (right) in comparison to external clinical aspect (picture on the left) (patient no. 25). The arrows show pathological ¹⁸F-FDG accumulation located in correspondence of the fistula (arrows)

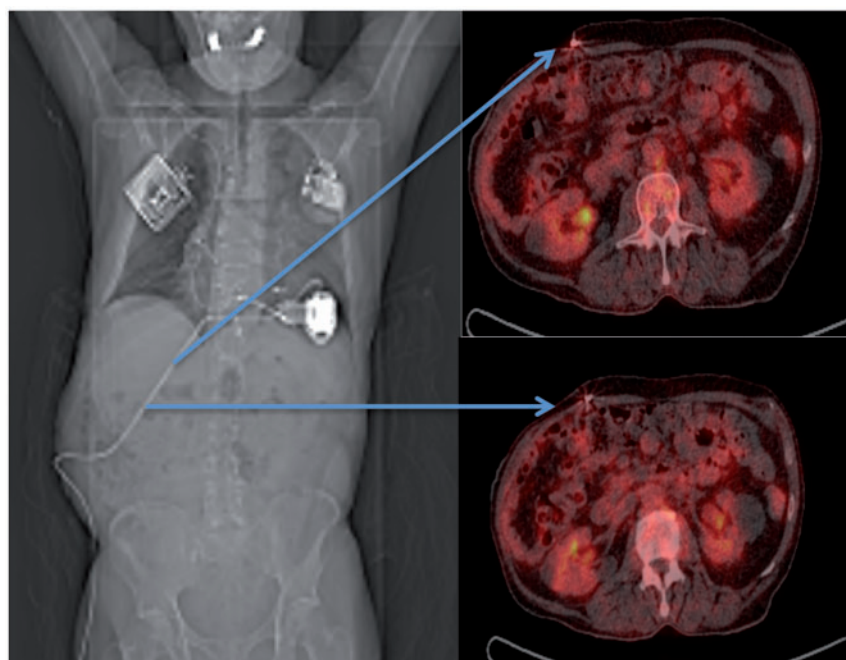


Figure 3 Frontal view of CT scan: normal ¹⁸F-FDG uptake of superficial and deep driveline (true negative finding, patient no. 33).

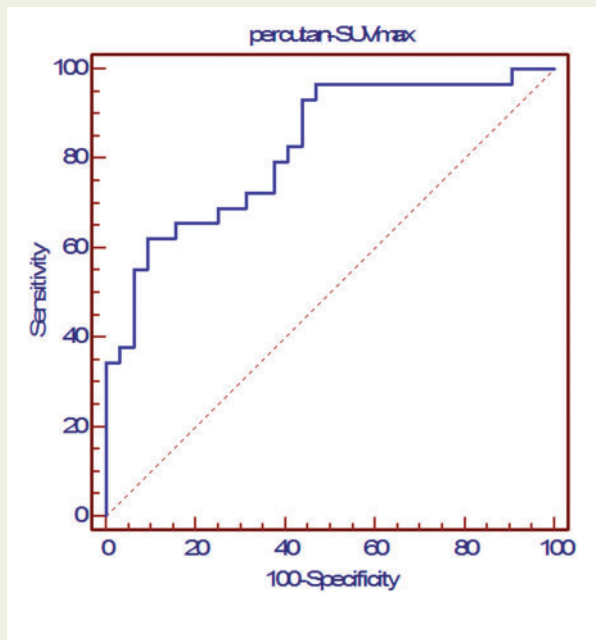


Figure 4 Receiver-operating characteristic curve of maximum standardized uptake value (SUV max) for the diagnosis of superficial driveline infection.

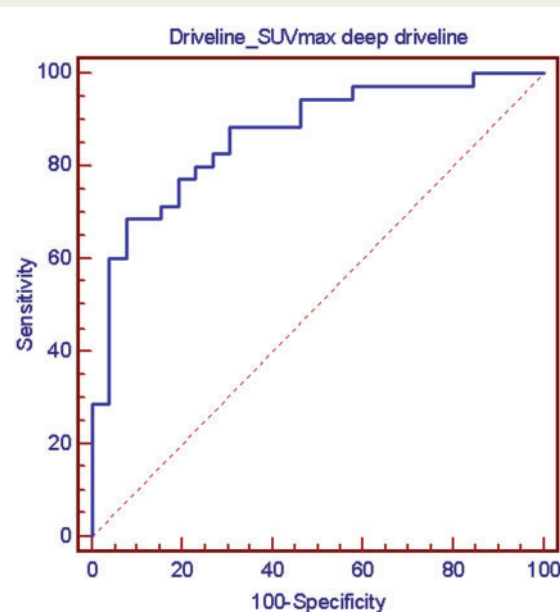


Figure 5 Receiver-operating characteristic curve of maximum standardized uptake value (SUV max) for the diagnosis of deep driveline infection.

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

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

		Median	Lower	Upper	Median	Lower	Upper	Median	Lower	Upper	P
		Total = 61	quartile	quartile	No infection = 32	quartile	quartile	Infection = 29	quartile	quartile	
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 ¹⁸F-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 ¹⁸F-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 ¹⁸F 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 ¹⁸F 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

¹⁸F-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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