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The value of fluorine-18 deoxyglucose positron emission tomography scans in patients with ventricular assist device specific infections[†]

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Abstract

BACKGROUND: Infections are major complications in patients with ventricular assist devices (VAD). Positron emission tomography with deoxyglucose marked by fluorine-18 (^{18}F-FDG PET/CT) is a diagnostic tool to scan for tissue with high metabolism as present in infections. The specificity of ^{18}F-FDG PET/CT to discriminate between infection and an aseptic reaction of the implanted device is not defined and its evaluation is the aim of this retrospective analysis.

METHODS: Until September 2015 a total of 100 patients underwent VAD implantations in our institution. Twenty-one patients (mean age 53.7 ± 14.3 years) had 29 PET-CT examinations for a suspected infection. All radiology reports were compared to clinical and intraoperative parameters. Infections were reported according to the guidelines of the International Society of Heart and Lung Transplantation. Follow-up was 222 days (range 107–484 days) after PET-CT scans and was complete in all patients.

RESULTS: In 7 patients PET-CT scan ruled out any VAD associated infection. Sixteen patients had a VAD specific infection. Two patients had false negative PET-CT scan results. The sensitivity of VAD-specific infections was 87.5%, the specificity 100%, the positive predictive value was 100% and the negative predictive value 86.7%. Seven patients had more than one PET-CT scans at different time points.

CONCLUSIONS: PET-CT scan findings showed a high specificity and positive predictive value for VAD-specific infections. Therefore, it may have the potential to guide the clinician in handling patients with infectious complications after VAD implantation.

Keywords: Ventricular assist device • Infection • Diagnostic • Computed tomography

INTRODUCTION

Long-term support with continuous flow left ventricular assist devices (CF-LVAD) has been shown to be beneficial for patients with end stage heart failure in both bridge to transplant (BTT) and destination therapy (DT) populations [1]. Latest Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report presents that second-generation CF-LVAD survival rates reach 80% in the first year after implantation but despite the survival benefit, infection continues to be a major complication [1]. Treatment modalities are tailored to severity and extent of infection which widely range from superficial wound infection to systemic inflammatory reaction syndrome but in defiance of surgical and medical intervention mortality still remains high.

To increase the survival outcome and reduce the need for explantation and exchange of LVADs, it is essential to detect the infection focus early and initiate appropriate treatment. However, definitive diagnosis is often challenging, particularly in early stages of VAD infection. Infections are major complications in patients with VADs and reasons for high urgency listing for transplantation. Whereas results after transplantation are comparable in patients with and without driveline infections (DI), large registry results showed that the mortality is higher in those with a device infection or mediastinitis [2].

Positron emission tomography with fluorodeoxyglucose marked by fluorine-18 (^{18}F-FDG PET/CT) is a non-invasive imaging modality that uses ^{18}F-FDG, a positron emitting glucose analogue, to assess glycolytic activity in cells, which is elevated in

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those that are subject to malignant or inflammatory processes. Thus, ^{18}F-FDG PET/CT has become a promising diagnostic tool to locate high metabolic foci such as in infection, allowing early detection and its extent. However, this methodology is limited due to its inability to discriminate between aseptic and septic nativity, potentially delaying or misleading adequate treatment.

The aim of this study was to evaluate the diagnostic value of ^{18}F-FDG PET/CT and its contribution to decision making in patients with ventricular assist device specific infections.

METHODS

Study population

We retrospectively analysed our experiences with CF-LVAD at our institution. Between January 2010 and December 2015 100 consecutive patients with end-stage heart failure underwent implantation of the HeartWare HVAD (Framingham, MA, USA).

In 21 patients, a total of 29 ^{18}F-FDG PET/CT scans were performed and included in this study.

PET/CT examinations were exerted if guideline-based primary diagnostic measures were inconclusive. Hence, all PET/CT scans were performed in the course of clinical routine and ensued either to substantiate clinical findings, detect location and extent of infection/inflammation.

Indication for FDG PET/CT included at least one of the following: persistent or recurrent clinical signs such as pain, fatigue, dyspnoea or oedema, neurologic issues after exclusion of cerebrovascular accidents and recalcitrant external signs of inflammation at the exit site of the driveline or surgery wound, unexplained persistent or undulating fevers above 38.0°C, unclear increase or persistent elevated infectious parameters or positive blood cultures. Patients were excluded of PET/CT examinations if informed consent was not signed or if claustrophobic. All patients met the inclusion criteria. No patient was excluded.

Scans of 7 patients who were admitted again due to another suspicious infection after clinical resolution of their first infection and with an infection free interval of >30 days without antibiotic treatment were handled as new cases. Mean time between the scans was 196.8 days (range 57–574 days).

Antibiotic treatment was initiated in all patients after manifestation of clinical infectious signs and if necessary treatment was adapted on the basis of laboratory results, guidelines and further clinical presentation. All patients had antibiotic treatment at the time of ^{18}F-FDG PET/CT examination.

VAD infection was defined using the International Society of Heart and Lung Transplant (ISHLT) classification of infections in VAD patients, which provides a delineation in VAD specific, VAD related, and non-VAD-related infection [3].

The most important procedures involved the assessment of swabs at exit site and wounds, swabs inside the body cavity along the driveline, and during surgical procedures such as Vacuum Assisted Closure therapy (V.A.C., KCI, San Antonio, TX, USA) or resternotomy. Furthermore, evidence took into account the examination of blood and urine cultures, sputum and respiratory secretion, as well as surgical samples after debridement, transplant, exchange or explant. Follow-up imaging included chest X-rays, CT scans and transthoracic or transoesophageal echocardiographic findings.

We reviewed the electronic medical records of all patients who underwent LVAD insertion and collected clinical data that included baseline demographics, medical histories and procedures as well as laboratory values, changes in clinical management after FDG-PET/CT results and patient outcome.

^{18}F-FDG PET/CT

Patients were instructed to fast for at least 4 h prior ^{18}F-FDG PET/CT examination. Blood glucose concentration of all patients were measured and noted before injection of ^{18}F-FDG. Mean blood glucose level at injection was 110 mg/dl (range 69–177).

^{18}F-FDG was injected intravenously at a mean dose of 351 MBq (range 312–406). After administration of ^{18}F-FDG, patients supplementary received 20 ml oral contrast agent Gastrografin (Bayer Vital GmbH, Leverkusen, Germany) in 1 litre of water.

During the uptake phase of an hour patients were seated in a warm waiting room to avoid muscle tension. If necessary, they were hydrated orally or intravenously up to 1 litre.

^{18}F-FDG PET/CT images were obtained using a hybrid PET/CT system (Gemini GXL10; Philips Medical Systems, Best, Netherlands). Image acquisition started with a non-enhanced whole-body low-dose CT (120 kV, 80 mA) for anatomical mapping and subsequent PET attenuation correction. Afterwards, total-body positron emission data were acquired in 3D mode with 90 s per bed position at the head, thorax, abdomen and 60 s at the legs in caudocranial direction. Overlap between consecutive bed positions was 50%.

Image reconstruction was automatically performed by the manufacturer-supplied system software with standard parameter modulations using the iterative 3D-line-of-response algorithm (144×144 matrix, spatial resolution of 8 mm full width at half maximum).

Additionally, a contrast enhanced CT (120 kV, 150 mA) with a mean dose of 140 ml Imeron 300 (Iomeprol, Bracco, Italy) was performed. CT image reconstruction included multiplanar reconstruction with axial, coronal and sagittal slices of 5 mm with an increment of 5 mm. Also an additional lung kernel window and maximum intensity reconstruction were generated.

All images were sent to a dedicated workstation equipped with a commercial software (Extended Brilliance Workspace, Philips Healthcare) for evaluation. Evaluation was performed by an interdisciplinary experienced staff team of 2 nuclear medicine physicians and 2 radiologists.

Results of the interdisciplinary consensus were recorded on a standardized report form.

The interdisciplinary team had access to medical history and was aware of the clinical symptoms of each patient but had no knowledge about the final diagnosis, subsequent clinical management or patient outcome.

PET images were visually evaluated for regions of increased radiotracer uptake compared with adjacent background. Lesions with significant ^{18}F FDG uptake well above background and outside of physiologic metabolically active areas were defined abnormal. Intense focal uptake was considered to be suspicious for infection whereas less intense diffuse uptake was considered to be rather non-infectious (Fig. 1).

The diagnostic value was validated by retrospectively comparing the ^{18}F-FDG PET/CT scan results with the final diagnosis. Final diagnosis was established upon microbiological, histological, intraoperative and clinical evidence and findings in follow-up images. Follow-up was 222 days (range 107–484 days) after PET/CT scans and was complete in all patients.

Statistical analysis

Categorical variables are expressed as frequencies, and continuous variables are reported as mean ± standard deviation for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. Normality test was performed using the Shapiro–Wilk test.

We conducted a paired *t*-test or Signed-Wilcoxon test for continuous variables, based on the distribution of the data. Statistical significance was assumed at a *P*-value less than 0.05. Data analysis was performed using SPSS 22 (IBM Corp, Armonk, NY, USA).

RESULTS

Baseline characteristics

We obtained 29 ^{18}F-FDG PET/CT scans of 21 subjects with suspected VAD-specific infection.

Six patients received 2 scans and 1 patient had 3 PET/CT examinations. All scans were considered as independent cases.

Baseline characteristics are reported in Table 1.

The main indication for ^{18}F-FDG PET/CT has been to locate infection focus ($n = 18$), evaluate the extent of infection ($n = 10$) and to rule out VAD related infection ($n = 1$). Main presenting symptoms or signs were local erythema ($n = 12$), fatigue ($n = 7$), abdominal/thoracic pain ($n = 7$), pus ($n = 7$), dyspnoea ($n = 6$), fever of unknown origin ($n = 5$), local swelling/oedema ($n = 2$) and neurological issues after cerebrovascular accident exclusion ($n = 2$).

Infection and laboratory results

Median time between LVAD implantation and first clinical signs of infection was 287 days (IQR: 99–586 days). Hematologic and inflammatory laboratory parameters are reported in Table 2.

Broad-antibiotic treatment was initiated in all patients after onset of infection and diagnostic measurements took place. Antibiotic treatment was adjusted by reference to further diagnostic and clinical presentation. None of our patients received antifungal therapy.

Between the day of indicative signs of infection and the day of the PET/CT examination the overall laboratory parameters did not significantly change except white blood cell count (10.6 ± 4.6 to 7.4 ± 2.6 Mrd/l, $P = 0.0031$).

Blood cultures were positive with pathogens detected such as *Staphylococcus aureus* in 3 patients (27.3%), *Staphylococcus epidermidis* in 2 patients (18.2%) and we identified *Enterococcus gallinarum*, *Serratia marcescens*, *Staphylococcus haemolyticus*, *Streptococcus gallolyticus*, *Streptococcus mitis*, *Streptococcus sanguinis* in 1 patient, respectively.

Wound swabs were positive with following pathogens ascertained: *S. aureus* in 8 patients (57.1%), *Coagulase negative staphylococcus* and *S. epidermidis* each in 2 patients (14.3%) and *Candida albicans*, *Escherichia coli*, *Staphylococcus capitis*, *Klebsiella oxytoca* in 1 patient, respectively. In 4 patients both blood cultures as well as swabs have been positive.

PET/CT diagnosis and diagnostic value

^{18}F-FDG PET/CT was performed 8 days IQR: 4–25 days) after onset of clinical signs or symptoms of infection and overall 292 days IQR: 106–591 days) after LVAD implantation. At the time of ^{18}F-FDG injection our cohort had a mean blood glucose level of 110 ± 25 mg/dl. Twelve patients (41.4%) did not receive a contrast agent due to an impaired kidney function, known hyperthyroidism or severe allergy to the contrast agent.

An abnormal ^{18}F-FDG uptake specific to the VAD has been identified in 17 cases (58.6%). In 12 cases (64.3%) the abnormal uptake has been associated with the VAD driveline, in 5 cases the infections were related to the pump (Table 3).

Table 1: Baseline characteristics of 21 patients with 18-F FDG PET/CT scans after CF-CAD implantation

	n = 21
Age, years	53.7 ± 14.3
Gender male	19 (90.5%)
Ischaemic cardiomyopathy	7 (33.3%)
Treatment strategy	
Bridge-to-transplant	16 (76.2%)
Bridge-to-candidacy	2 (9.5%)
Destination therapy	3 (14.3%)
Arterial hypertension	6 (28.6%)
Diabetes mellitus	7 (33.3%)

CF-CAD: continuous flow left ventricular assist devices.

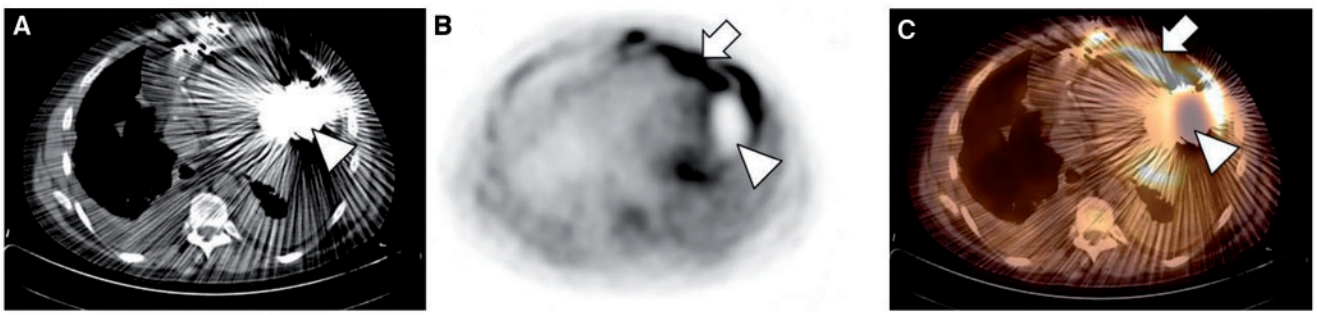

Figure 1: Example of a positive ^{18}F-FDG PET/CT scan in a patient with 2 HeartWare HVAD devices (BiVAD) and a VAD specific pump infection. Axial CT image (**A**) shows the LVAD (arrow head) with significant metal artifacts. The corresponding PET image (**B**) and the fused PET/CT image (**C**) show a photopenic area in the position of the LVAD and an abnormal elevated ^{18}F-FDG uptake in the surrounding infected tissue (arrow). LVAD: left ventricular assist devices; VAD: ventricular assist device.

Table 2: Comparison of the laboratory results between the day of onset of infection and the day of PET/CT examination

	Onset infection (mean ± SD)	PET/CT exam (mean ± SD)	*P*-value
Hb (g/dl)	10.3 ± 1.9	10.3 ± 1.3	0.882
WBC (Mrd/l)	10.6 ± 4.6	7.4 ± 2.6	0.01
CRP (mg/l)	74.1 ± 81.4	52.8 ± 65.3	0.085
LDH (U/l)	322.2 ± 143.8	282.5 ± 78.4	0.075
INR	2.8 ± 0.7	3.0 ± 1.1	0.209

Hb: haemoglobin; WBS: white blood cell count; CRP: C reactive protein; LDH: lactate dehydrogenase; INR: international normalized ratio.

The definitive diagnosis in 29 cases were ascertained as VAD specific infections present in 16 cases (55.2%) and absent in 13 cases (44.8%). Two patients had false negative PET/CT examination results, with clinical evidence of deep driveline infection and device infection.

The first patient was a 36 year old male who had an LVAD and temporary RVAD implanted for acute myocarditis in INTERMACS level I. After RVAD explantation he recovered well and was discharged home. Six months later he was readmitted with signs of infection at the driveline exit. The PET/CT scan was done for the evaluation of the extent of infection. No abnormal ^{18}F-FDG uptake was seen. Despite the negative result but due to the local infection a Vacuum Assisted Closure (VAC) therapy was initiated. Intraoperatively the infection extended to the mid of the driveline. Wound swabs were positive for *E. coli*.

The second patient with false negative PET/CT scan results was a 52 year old male patient who suffered from myocardial infarction and cardiogenic shock. After extracoporeal membrane oxygenator and LV-vent implantation an LVAD and temporary RVAD were implanted. Six weeks after the patient developed signs of a presternal wound infection and a VAC therapy was initiated. To exclude a VAD specific infection a PET/CT scan was performed excluding a VAD specific infection. However, during change of the VAC dressing, there was a high suspicion of a deep sternal wound infection affecting the device. Wound swabs from the outflow graft confirmed infection of the device with *S. epidermidis and C. albicans.*

The results of the definitive diagnosis are summarized in Table 4. The sensitivity of VAD specific infections is 87.5%, the specificity is 100%, the positive predictive value is 100% and the negative predictive value is 86.7%. For the 18 patients who had no obvious VAD specific infection but were examined to locate the infectious focus, the sensitivity was 77.8%, specificity 100%, positive predictive value 100% and the negative predictive value 81.8%.

In the cohort of 7 patients with more than one scan the mean time between the scans was 196.75 days (range 57–574 days). In 1 patient both scans were not VAD associated but showed abnormal FDG uptake at different locations respectively. In 4 patients either their first or their second scan showed FDG uptake associated with VAD infection—yet the other scan showed infections at different locations. In 2 patients the 2 infections seen in the PET/CT examinations were associated with the VAD but with a mean time of 205.6 days between the scans without antibiotic treatment, making it highly unlikely to be the same underlying infection as the prior one.

Table 3: Infections classified according to the recommendations by the International Society for Heart and Lung Transplantation (ISHLT)

Infection according to ISHLT classification	*n* = 29 cases
VAD specific infections	16 (55.2%)
Pump and/or cannula infection	5 (17.2%)
Pocket infections	0
Driveline infections	
Minor exit site erythema	1 (3.4%)
Superficial infection	5 (17.2%)
Deep infection	5 (17.2%)
VAD related infections	6 (20.7%)
Infective endocarditis	0
Bloodstream infections	4 (13.7%)
Mediastinitis	2 (6.9%)
Non-VAD related infections	7 (24.1%)
Lower respiratory tract infection	0
Cholecystitis	0
Clostridium difficile infection	0
Other	7 (24.1%)

Table 4: Results of PET/CT examination for VAD specific infections

	PET CT positive	PET CT negative	Total
VAD specific infection present	14	2	16 (55.2%)
VAD specific infection absent	0	13	13 (44.8%)
Total	14 (48.3%)	15 (51.7%)	29 (100%)

The PET/CT examination helped the clinicians change the medical regimen in 12 patients, thus contributed to decision making: In 9 cases (64.3%) a surgical procedure has been initiated, in 4 cases (28.6%) results of the PET/CT examination led to prolongation of the antibiotic treatment and in another 4 patients (28.6%) the results from the examination led to high urgency listing for transplantation. In those 4 particular patients who were transplanted 2 had deep driveline infections and 2 had device infections. In all 4 patients the results from the PET/CT examination correlated well with the extent of infection during the transplant procedure. The first patient with the device infection suffered from a methicillin resistant *Staphylococcus aureus* and was under persistent vancomycin treatment on the waiting list. During the transplant procedure multiple abscesses were noted and the patient was vasoplegic requiring high doses of catecholamines. He died 5 days after the transplantation due septic complications. The second patient with a device infection underwent the transplantation without any complications. For prevention of a mediastinitis we inserted drains to provide continuous flush for 5 days postoperatively. Concomitantly, we gave broad-spectrum antibiotics. Two years after heart transplantation the patient is doing well and is full-time working without any infectious complications. In the 2 patients who were listed for deep

driveline infections and subsequently got transplanted the extent of the driveline infection has been confirmed in both cases. The intra- and postoperative course of both patients was uneventful and no late infectious complications occurred.

DISCUSSION

This study uses the recommendations of the International Society for Heart and Lung transplantation to report infections in patients with ventricular assist devices. The main findings of our study are that results from ^{18}F-FDG PET/CT examination showed a high and positive predictive value for VAD specific infections.

Ventricular assist devices and infections

Ventricular assist devices are nowadays an established treatment strategy for patients with end-stage heart failure awaiting heart transplantation or for patients who have contraindications for transplantation (destination therapy). Infections associated with the VAD still account for morbidity and mortality in these patients. One year after VAD implantation up to 30% of patients experience any kind of VAD associated infection [1]. In 2011 the International Society for Heart and Lung Transplantation published a consensus-based expert opinion to provide standard definitions of infections in VAD patients. These have been adapted from existing standardized definitions based on the pathophysiology of equivalent infections in prosthetic valve infections and divided into 3 sections: VAD-specific infections, VAD-related infections and non-VAD infections. VAD-specific and VAD-related infections are difficult to treat and remain a major cause of death [4]. The effect of VAD-specific and VAD-related infections depends on the site and the severity of the infection. Mortality rates of up to 70% have been observed in patients with VAD-related infective endocarditis or mediastinitis involving the pump [5–9]. Morbidity and mortality, however, is not only increased during VAD therapy, but also following heart transplantation in recipients bridged by a VAD with specific infectious complications. A study by Healy and colleagues investigated outcome in 15 253 heart transplant recipients after status 1A listing using the United Network for Organ Sharing (UNOS) database. They compared patients with and without VAD related complications and demonstrated that 1-year survival is comparable for most complications on VAD, yet heart transplant recipients with a device infection had a worse 1-year post-transplant survival [2]. A device infection is a major risk factor for dismal post-heart transplant survival or may even be a relative contraindication for heart transplantation. Thus, it is of great importance to quantify a VAD specific infection and stratify patients accordingly. An accurate diagnosis of the infection extent may either change the listing and treatment strategy, e.g. pump exchange, on the waiting list or even change the treatment peri- and post-transplant in case of device infection. In our series 1 patient with device infection on PET/CT received perioperative escalated antibiotic treatment once the organ was accepted and continued after the transplantation. In addition, drains to flush the mediastinum were inserted and kept for 5 days, postoperatively. This patient had in contrast to a previous heart transplantation into a similar situation with device infection an uneventful postoperative course.

CT and ^{18}F-FDG PET/CT examination

Imaging has a particular role in revealing new inflammatory change in the mediastinum, large valve vegetations and cannula insertion infections. It is also used to characterize sternal wound infections and the extent of deep-seated infections.

The diagnosis and treatment of VAD related infections remain challenging and controversial [10, 11]. Microbiologic data obtained from the driveline exit site or blood samples can confirm the presence of infection but fail to determine its precise location or extent. Morphologic imaging alone may be unreliable because of the presence of metal related artefacts. PET lacks anatomic landmarks that allow exact localization of infection. Analysis of planar acquisitions of VAD patients is difficult because of artefacts generated by the metallic device. The use of ^{18}F-FDG PET/CT allows precise localization of infection and accurate interpretation of images. Although ^{18}F-FDG PET/CT registration mismatch may occur in areas of movement, such as the chest and upper abdomen, all our ^{18}F-FDG PET/CT scans provided excellent anatomic mapping of the infectious foci.

Device-specific deep infection needs to be diagnosed or at least excluded if septicaemia occurs in VAD patients. In the context of recurrent device specific infections, ^{18}F-FDG PET/CT is a non-invasive diagnostic tool with an acceptable radiation exposure. Furthermore, ^{18}F-FDG PET/CT allows whole-body imaging with simultaneous examination of the VAD, enabling the detection of unsuspected sites of distant infection.

To date, not much literature is available on the use of ^{18}F-FDG PET/CT examination in context with VAD associated infections and little is known about the diagnostic value of this evaluation. Previous reports differ in implant techniques and protocols to diagnose and report infections making comparisons difficult. However, a recent study by Dell'Aquila and colleagues described a sensitivity of 100% and a specificity of 80% of ^{18}F-FDG PET/CT examination for detecting infections of VAD components in their cohort [12]. In contrast to our study, infection was not clearly defined making direct comparison difficult. In our series, we found a specificity of 100% and a sensitivity of 87.5%. Two patients had false negative ^{18}F-FDG uptake despite clinical evident deep infection. Circumstances related to these false negative results remain unclear. Of note, in patients who had more than one ^{18}F-FDG PET/CT examination we were able to quantify clinical changes by the radiologic evaluation. This highlights the value in clinical practice as the specificity and the positive predictive value for VAD specific infections have been 100%. Especially patients who have a known infection, as in our series, may profit from ^{18}F-FDG PET/CT examination. ^{18}F-FDG PET/CT examination has the potential to confirm an infection as well as locate and quantify the extent of the infection.

The use of antibiotics prior to PET/CT examination may have an impact on ^{18}F-FDG uptake. Antibiotic therapy has been shown to cause a significant decrease in ^{18}F-FDG uptake in other conditions [13]. However, this puts our results into real-world context as it is common practice for antibiotics to be given for a suspected VAD specific infection. As far as it is possible to draw conclusions we neither found a correlation between time and use of antibiotic treatment before PET/CT examination nor relevant impact on evaluation results.

Isotope labelled leukocytes examinations were described in small series of patients [14, 15]. In our institution PET/CT examinations are the only nuclear radiologic modality used to evaluate

VAD associated infections. Therefore, it was not possible and the current study was not intended to compare PET/CT examinations to other modalities for the diagnosis of VAD associated infections. Further, to the best of our knowledge, there is no study available to date comparing both modalities for VAD associated infections. In general, costs for PET/CT examinations are higher, half-value time lower and spatial resolution higher, which may improve the ability to quantify the extension of the infection. However, as there is no study available comparing both modalities the superiority of one over the other remains unclear.

CONCLUSION

^{18}F-FDG PET-CT scan results showed a high specificity and positive predictive value for VAD specific infections. Therefore, it may have the potential to guide the clinician in handling of infectious complications after VAD implantation.

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