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^{18}F-Fluorodeoxyglucose Positron Emission Tomography / Computed Tomography in Left-Ventricular Assist Device Infection: Initial Results Supporting the Usefulness of Image-Guided Therapy

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ABSTRACT

Background: Accurate definition of the extent and severity of left-ventricular assist device (LVAD) infection may facilitate therapeutic decision making and targeted surgical intervention. Here, we explore the value of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) for guidance of patient management.

Methods: Fifty-seven LVAD-carrying patients received 85 whole-body ^{18}F-FDG PET/CT scans for the work-up of device infection. Clinical follow-up was obtained over a period of up to two years.

Results: PET/CT showed various patterns of infectious involvement of the 4 LVAD components: driveline entry point (77% of cases), subcutaneous driveline path (87%), pump pocket (49%) and outflow tract (58%). Driveline smears revealed staphylococcus or pseudomonas strains as the underlying pathogen in a majority of cases (48 and 34%, respectively). At receiver-operating characteristics analysis, an ^{18}F-FDG standardized uptake value (SUV) >2.5 was most accurate to identify smear-positive driveline infection. Infection of 3 or all 4 LVAD components showed a trend towards lower survival vs infection of 2 or less components ($p=0.089$), while involvement of thoracic lymph nodes was significantly associated with adverse outcome ($p=0.001$ for nodal SUV above vs below median). Finally, patients that underwent early surgical revision within 3 months after PET/CT (n=21) required significantly less inpatient hospital care during follow-up when compared to those receiving delayed surgical revision (n=11; $p<0.05$).

Conclusion: Whole-body ^{18}F-FDG PET/CT identifies the extent of LVAD infection and predicts adverse outcome. Initial experience suggests that early image-guided surgical intervention may facilitate a less complicated subsequent course.

Key words: left ventricular assist device, PET/CT, ^{18}F-fluorodeoxyglucose, device infection

INTRODUCTION

Left-ventricular assist device (LVAD) implantation improves survival and quality of life in end-stage heart failure, and it is increasingly employed for destination therapy as an alternative to heart transplantation (*1-4*). Despite continuous technological improvement, device infection remains a major complication after LVAD implantation (*5,6*), because the driveline provides a transcutaneous pathway for entrance, growth and spread of pathogens towards internal components of the system and beyond. While the driveline entry point at skin level is readily accessible, the diagnostic and therapeutic management of internally spreading LVAD infection is challenging.

Positron emission tomography / computed tomography (PET/CT) with the glucose analogue ^{18}F-fluorodeoxyglucose (FDG), which is avidly taken up by inflammatory leukocytes and infectious pathogens, is an emerging technique for imaging of cardiovascular implant infection (*7*). The benefit of PET/CT over conventional leukocyte scintigraphy is its higher sensitivity and faster imaging protocol, while morphologically driven techniques such as echocardiography and computed tomography are limited by artifacts from the implant material and magnetic resonance imaging is not an option. The feasibility and diagnostic accuracy of PET/CT for detecting LVAD infection has been reported in small patient groups by several centers, and it was recently summarized in a meta-analysis (*8*). This is a first step towards broader clinical implementation, which should be amended by demonstration of a link between PET/CT results and adverse outcome, and by data showing that outcome can be improved when imaging is used to guide therapy (*9*).

Here, we report about the use of ^{18}F-FDG PET/CT for clinical guidance in patients with advanced LVAD infection in our large LVAD referral center (*1,4,10*). We speculated that ^{18}F-FDG PET/CT will not only identify subjects at elevated risk, but that it will also guide surgical therapy to improve the subsequent course. To test our hypothesis, we obtained clinical information, imaging results and follow-up in a comparatively large sample of LVAD recipients having undergone PET/CT.

METHODS

Study Group

The study group consisted of 57 LVAD recipients, which were consecutively referred for PET/CT between July 2015 and April 2017, for clinical assessment of extent and severity of device infection due to persisting local or systemic signs of infection. Demographics and other patient characteristics are listed in table 1. Nineteen patients received repeated scans after 154±11 days of the prior scan (range 39-343 days), in order to re-evaluate for suspected reappearance or progression of infection. Between scans, there was a change of antibiosis in all but one of the repeat imaging cases, 8 had anti-infective surgery and 5 had a complete change of the device. The resulting total of 85 scans was used for correlative analysis of image-derived and clinical parameters at the time of PET/CT, where indicated (scan-based analysis). All other analyses, including outcome analyses, were performed on a patient-by-patient base (n=57). All patients gave written informed consent for PET/CT imaging. The ethical committee of MHH was informed of the retrospective analysis of scan results and clinical outcome and waived formal review.

PET/CT Imaging and Data Analysis

Following 6 hours of fasting and confirmation of blood glucose levels <8 mmol/l, 262±64 MBq of ^{18}F-FDG were injected intravenously. After an uptake time of 60 minutes, whole body PET scans were acquired using a Siemens Biograph mCT 128 (Siemens Healthineers, Erlangen, Germany) with continuous table motion, as previously described (*11*). A non-enhanced low-dose CT was acquired for anatomical co-registration and attenuation correction. Non-corrected and attenuation corrected images were reconstructed using a resolution recovery iterative algorithm. Foci of increased ^{18}F-FDG uptake were visually identified by two experienced observers. A focus was graded as positive if it was significantly elevated versus background in the regions of the device. Consensus was obtained in case of discrepancies. All foci of uptake were confirmed as elevated versus background on non-attenuation corrected images, in order to avoid artefacts induced by dense implant material (*12*). Using volume-of-interest technique, peak standardized uptake values (SUVs) were obtained from attenuation corrected scans in order to quantify ^{18}F-FDG uptake of each focus. For localization of LVAD-specific infection, the LVAD was subdivided into 4 components (consistent with ISHLT recommendation (*13*)): driveline entry point, subcutaneous driveline pathway, pump pocket, and outflow tract (figure 1A). Additionally, SUVs were obtained for regions remote from the LVAD. This included blood pool (aorta) and liver to measure background, hematopoetic organs (spleen, bone marrow) which may be activated in systemic infection, and thoracic lymph nodes with elevated ^{18}F-FDG uptake. Finally, scans were systematically analysed for other, LVAD-related or non-related inflammatory foci.

Clinical Data, Driveline Smears and Follow-up

All LVAD recipients at Hannover Medical School undergo tight clinical follow up with outpatient visits at least every 3 months. Wound smears of the driveline exit side were available at the time of PET/CT, performed by highly experienced nurses according to standardized protocol. Based on this protocol, 99% of all driveline exit sites of newly implanted LVAD patients show a sterile result, confirming that contamination by normal skin culture is successfully avoided. Regular clinical visits enabled gathering of clinical follow-up data from hospital records, which were obtained for all patients for 2 years following PET/CT, or until occurrence of an event or another PET/CT (in case of scan-based analysis only). Recorded events included death, heart transplant, LVAD replacement, and any other surgical anti-infective intervention. Additionally, the length of required hospital stays for inpatient care after PET/CT was recorded, and systemic inflammatory markers and smear results from driveline entry points were taken from patient records at the time of PET/CT.

Statistical Methods

Data were analysed using MedCalc software (Ostend, Belgium). Results are reported as average ± standard deviation for continuous variables, or median and range for non-normally distributed variables. Groups of normally distributed variables were compared using t-test. Non-parametric Mann-Whitney U-test was employed if normal distribution was not confirmed. Receiver operating characteristics (ROC) analysis was used to identify the relationship between SUV at the driveline entry site and results of microbial smears as a reference. And finally, Kaplan-Meier analysis and log-rank test were employed to identify

predictors of outcome during follow-up. A p-value of <0.05 was considered statistically significant.

RESULTS

^{18}F-FDG PET/CT identifies extent and severity of LVAD infection

All scans showed visually detectable foci of ^{18}F-FDG uptake suggestive of LVAD-specific infection. Multiple LVAD components were involved in the majority of scans: Two in 29 scans (34%), three in 28 (33%) and all four in 21 (25%). This confirms the advanced stage of infection in the studied patient group. Most often, elevated ^{18}F-FDG uptake was found along the driveline (entry point, n=65, 77% of scans; subcutaneous driveline pathway, n=74, 87% of scans), while intrathoracic components were also frequently involved (pump pocket, n=42, 49% of scans; outflow tract, n=49, 58% of scans). SUVs for foci at the 4 components are summarized in table 2, showing a decline along the probable pathway of infection with highest values at the driveline entry and lowest at the outflow tract. Figure 1B-D shows PET/CT images representative for infection of each of the 4 LVAD components.

Driveline entry point smears were available for 83/85 studies. Pathogens were identified in n=62 (75% of scans), and revealed staphylococcus or pseudomonas strains in the majority (n=30, 48% and n=21, 34% of positive cases). ROC analysis revealed an area under the curve of 0.71 (p=0.004) for detecting smear-positive driveline entry point infection by elevated FDG uptake. A peak SUV of >2.5 was identified to be most accurate (Youden's Index 0.41), yielding a sensitivity of 87% and specificity of 59%.

Upon analysis of remote regions, elevated focal FDG uptake in draining intrathoracic lymph nodes was a frequent LVAD infection-related finding (n=56, 66% of cases). A

representative PET/CT-scan showing thoracic lymph node involvement is shown in figure 2. Of note, extent and severity of FDG uptake at LVAD components was not correlated with ^{18}F-FDG uptake in hematopoetic organs or systemic inflammatory markers at the time of PET/CT (C-reactive protein, p=0.38; leukocyte count, p=0.34). Non-LVAD infection related sites of ^{18}F-FDG uptake included the sternum, various joints, ribs and muscles. No septic emboli were identified in the study group.

PET/CT results predict adverse outcome

Fourteen of 57 patients (25%) died during follow up. Death certificates identified sepsis as underlying cause in 7, and multiple organ failure in 5 patients. Two patients died during or immediately after heart transplantation. The time between the last PET/CT and death ranged from 13 to 466 days, with a median of 55 days. Ten patients underwent heart transplantation at 72-334 days after PET/CT (median, 158 days) and were censored at the time of transplantation for survival analysis. Among various image-derived parameters, Kaplan-Meier analysis identified a trend towards adverse outcome if infection involved 3 or all 4 LVAD components (p=0.089 vs 2 or less components, figure 3A). Also, involvement of thoracic lymph nodes was significantly associated with adverse outcome (p=0.001 for nodal SUV above vs below median, figure 3B). Other markers, including SUV of any individual LVAD component, average SUV of all components, uptake in spleen or bone marrow, or detection of non-LVAD infection sites were not significantly associated with adverse outcome.

Early surgical revision after PET/CT is associated with reduced in-patient care

Surgical anti-infective procedures were performed in 32 patients, within the first year after PET/CT. This included replacement of LVAD components in 24 patients (at 3-108

days after PET/CT, median 15 days), and targeted vacuum wound drainage in the other cases. Among those 32, a group of 21 patients received early surgery within the first 3 months after PET/CT (group 1; surgery assumed to be driven by scan results), while a group of 11 patients underwent surgical procedures later than 3 months after PET/CT, after interval adaptation of medical therapy (group 2; surgery assumed to be independent of scan results). The remainder of 25 patients, which did not receive anti-infective surgery, were disregarded for subsequent analysis because they reflect a heterogeneous mixture of less complicated cases (where continued or adapted systemic antibiotics were considered to be sufficient; n=14), more severely affected cases which died without surgery (n=5), or cases which received cardiac transplantation (n=6).

Survival analysis showed no significant difference between groups 1 (5 deaths; 24%) and 2 (4 deaths; 36%) during follow up. But the recorded overall length of inpatient care time during the first year after PET/CT differed significantly, showing significantly less inpatient days in group 1 (99±87 vs 158±130 days for group 2, p=0.016; figure 4).

DISCUSSION

In summary, our results confirm that ^{18}F-FDG PET-CT enables the detection of localization, extent and severity of LVAD-specific infection. ^{18}F-FDG also identifies LVAD infection-related involvement of thoracic lymph nodes. Importantly, PET/CT results can be used to identify subjects at highest risk of adverse outcome. If targeted surgical revision of infected components is performed early after PET/CT, and thus assumedly guided by imaging results, then the length of subsequent in-hospital stays is significantly reduced. To our knowledge, this report includes the largest single-center sample of FDG PET/CT scans

in subjects with LVAD infection to date. It should be used as a foundation for subsequent prospective trials investigating the effect of PET/CT-guided anti-infective surgical therapy in the management of LVAD recipients with advanced infection.

The instantaneous risk for LVAD infection peaks initially in the post-surgical phase <30 days after implantation (*5*). In subsequent times, it remains constantly elevated at a lower level (*5*), contributing to a steady increase of cumulative risk with increasing duration of LVAD support. Our study does not cover the early post-surgical phase. Instead, it focuses on the value of ^{18}F-FDG PET-CT in later-onset infections, which are nevertheless known to have a significant effect on survival (*5,14,15*). Patients included in this analysis were in an advanced state of infection, as confirmed by the high prevalence and extent of positive scans (100% with at least one infected LVAD component, 92% with at least 2 and >50% with 3 or 4 components), by the high prevalence of LVAD-related lymph node involvement, by the persistence of infection despite systemic antibiotic therapy prior to PET/CT, and by the occurrence of all but one deaths within the first 150 days after PET/CT (see figure 3). This likely explains our observation that involvement of thoracic lymph nodes as the infection-related drainage site from internal LVAD components had the strongest prognostic value, while involvement of internal components itself showed a trend towards significant prognostic value, but did not have the same discriminatory prognostic power as nodal involvement or as recently reported by another group in a different and smaller sample, where the focus was on early detection (*16*).

The state of advanced LVAD infection also represents a situation where effective therapy is difficult and where it may most strongly benefit from guidance by imaging. It is generally assumed that LVAD infection spreads from the driveline entry point towards the

inner components of the system. A revision or change of the driveline is less complicated and risky than a complete exchange of the LVAD system. However, driveline revision can only be a meaningful therapy if it is done before the infection has reached the aggregate. Here, the comprehensive PET/CT information is useful to guide surgical revision to the infected LVAD components. In our patients, e.g., an infection at the aggregate was found in >50% of cases, suggesting that a pure driveline-directed therapy would be incomplete for the majority. Importantly, our analysis also shows that if targeted anti-infective surgery was pursued early after PET/CT, then there was less need for inpatient care in the subsequent year when compared to individuals which did receive surgery at a later time (where results of PET/CT were not actual anymore). This suggests that the greatest value of ^{18}F-FDG PET/CT may lie in guidance of surgical therapy to the appropriate, infected LVAD components.

It should be noted that PET/CT had a relevant impact on clinical patient management in our patient group, because it not only guided targeted anti-infective surgery in a subset of patients, but also lead to prioritization for transplantation in some cases, or to continued or adapted antibiotic therapy, presumably in those cases where infection was considered less severe. Of note, exact duration of antibiotic therapy was not completely documented in our retrospective analysis and repeat imaging was only obtained if recurrence or progression of infection was suspected, so that valid conclusion about the effect of antibiotics on detection rate of PET/CT cannot be derived from our study.

Some further limitations of our work need to be recognized: First, this was a retrospective single-center analysis, with all its inherent limitations. Although the sample size is larger than that of previous original work reporting on PET/CT in LVAD infection, the

results still represent local experience of our referral center. Bias may have been introduced by the clinical use of PET/CT in a more advanced state of infection and by the resulting lack of cases with early or no infection for comparison. The normal distribution of ^{18}F-FDG around the LVAD and its time course after implantation remain poorly defined and cannot be derived from our study group. Also, the length of hospital stay had to be used as a surrogate marker of outcome (*17*) after anti-infective surgical revision, because differences in survival were not detectable, probably due to limited power of the still small number of subjects. And, the formation of groups based on time between PET/CT and surgery is based on the assumption that an earlier scan will have a more direct effect on surgery, but this assumption cannot be proven due to the retrospective design. Likewise, factors other than time after PET/CT may have confounded the differences in subsequent hospital stay. Therefore, the results of the present study should be seen as a hypothesis generation. This hypothesis - that PET/CT-guided, targeted anti-infective therapy may be beneficial in LVAD infection - clearly needs to be confirmed in a subsequent prospective trial.

Second, this work did not focus on establishing diagnostic accuracy of ^{18}F-FDG PET/CT in LVAD infection. Most prior studies have focused on accuracy of the test, suggesting high sensitivity but lower specificity (*8,18-20*), and superiority when compared to white-blood cell scintigraphy (*21*). Yet, determination of diagnostic accuracy is highly dependent on validity and robustness of the reference standard (*22*), which is not free of challenges in LVAD infection, where the proof of pathogens in culture is complicated by sampling error and often longstanding antibiotic therapy (*23*), and where indirect clinical parameters are proposed as surrogate markers for the presence of infectious pathogens according to ISHLT consensus (*13*). We included an analysis of the driveline entry point as

an area which is easily accessible for smears, and used positive proof of pathogens from smear as the gold standard. Thereby, we were able to determine high sensitivity and lower but acceptable specificity of PET/CT, both well in the range of prior studies (*8*). Specificity of ^{18}F-FDG for infection is generally limited, because the tracer does not detect bacteria directly and is taken up by all metabolically active leukocytes. Hence, sterile inflammation cannot be distinguished from infection. The early post-surgical phase, where sterile inflammation is frequently observed due to reparative mechanisms, was excluded in our study. But despite focusing on late-onset LVAD infection, it should be noted that subjects in our study were treated with antibiotics and may have had local antiseptic wound care, which may have reduced bacteria beyond detectability by smear while inflammatory cells taking up ^{18}F-FDG may still have been present. These factors may have further contributed to compromised specificity. Also, it should be noted that we did not include the driveline pathway, pump pocket or outflow tract in this analysis because structured data on pathogen detection were not available for the internal locations. Nevertheless, while our sub-analysis of accuracy may be limited, the major focus of this work was to generate initial data on outcome prediction and modification by imaging and image-guided therapy, and the prognostic value and reduction of inpatient care are observations, which stand as they are.

CONCLUSION

The present analysis of a comparatively large patient sample from a single LVAD referral center confirms that ^{18}F-FDG PET/CT identifies the extent of advanced LVAD infection and predicts adverse outcome. Initial experience also supports the notion that

early image-guided surgical intervention may facilitate a less complicated subsequent course. The present work provides a foundation for the design of subsequent prospective studies to confirm this hypothesis.

SOURCES OF FUNDING

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DISCLOSURES

The authors declare that they have no conflicts of interest.

KEY POINTS

QUESTION: Can ^{18}F-FDG PET/CT guide surgical therapy in left-ventricular assist device (LVAD) infection?

PERTINENT FINDINGS: ^{18}F-FDG PET/CT yields accurate information about presence, severity and extent of LVAD infection, which predicts adverse outcome. If LVAD recipients undergo surgical treatment early after (and guided by) PET/CT, they require less inpatient care in the subsequent year.

IMPLICATIONS FOR PATIENT CARE: ^{18}F-FDG PET/CT-guided surgical therapy in LVAD infection may improve outcome and reduce complicated patient courses.

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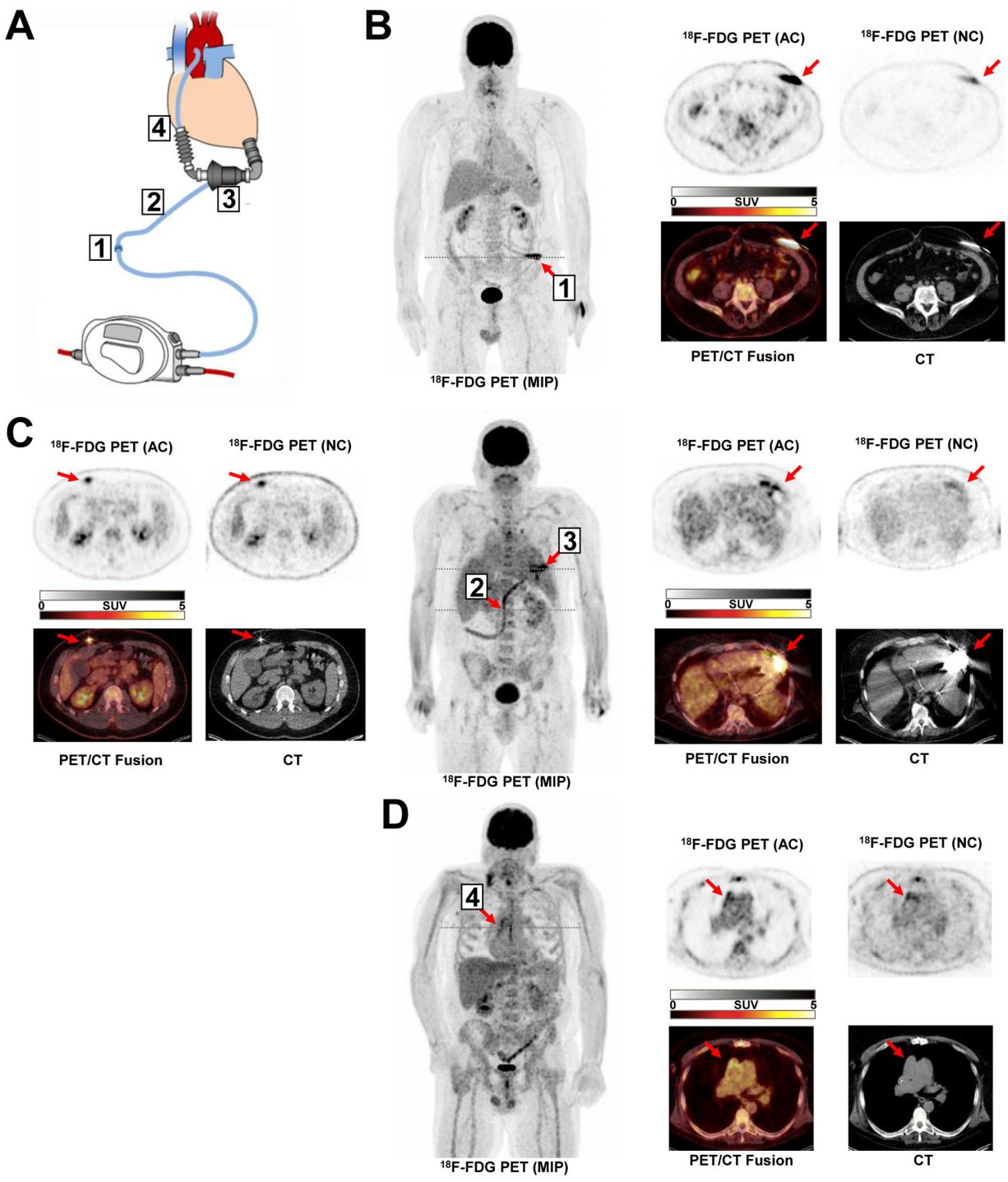

Figure 1: Detection of left ventricular assist device (LVAD) infection by ^{18}F-fluorodeoxyglucose (FDG) PET/CT. (A) Schematic display of LVAD system, subdivided into 4 components: Driveline entry point (1), subcutaneous driveline path (2), pump pocket (3)

and outflow tract (4). (B) Case with infection restricted to driveline entry point at left abdominal wall (1). (C) Case with infection of subcutaneous driveline path (2, left) and pump pocket (3, right). (D) Case with infection of outflow tract (4). PET, positron emission tomography; CT, computed tomography; AC, attenuation corrected images; NC, noncorrected images; SUV, standardized uptake value; MIP, maximum intensity projection.

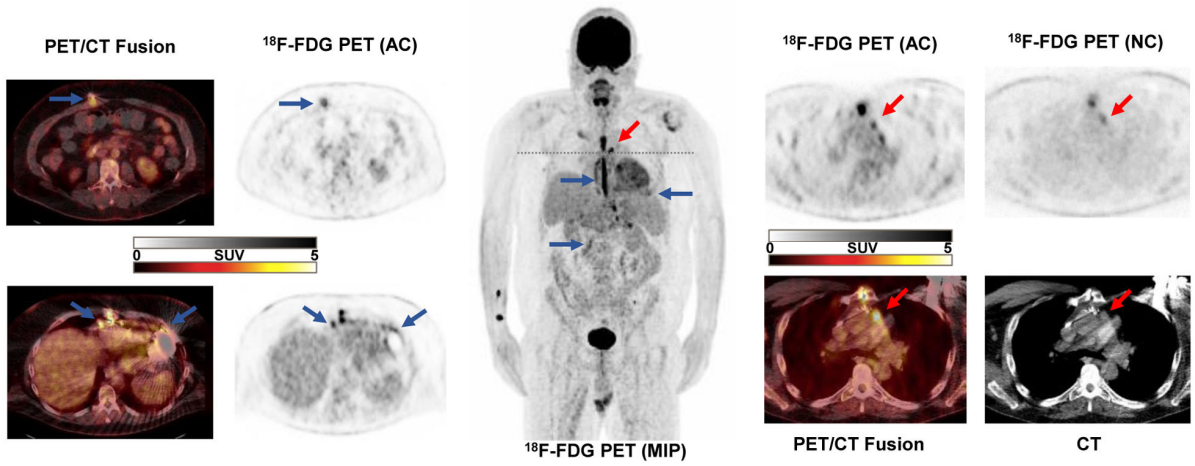

Figure 2: ^{18}F-fluorodeoxyglucose (FDG) PET/CT identifies thoracic lymph node involvement in left ventricular assist device (LVAD) infection. Shown is a case with infection of subcutaneous driveline path (blue arrows, left, top), pump pocket and outflow tract (blue arrows, left, bottom). Additionally, mediastinal lymph nodes in the upper thorax show elevated ^{18}F-FDG uptake (red arrow, right). PET, positron emission tomography; CT, computed tomography; AC, attenuation corrected images; NC, noncorrected images; SUV, standardized uptake value; MIP, maximum intensity projection.

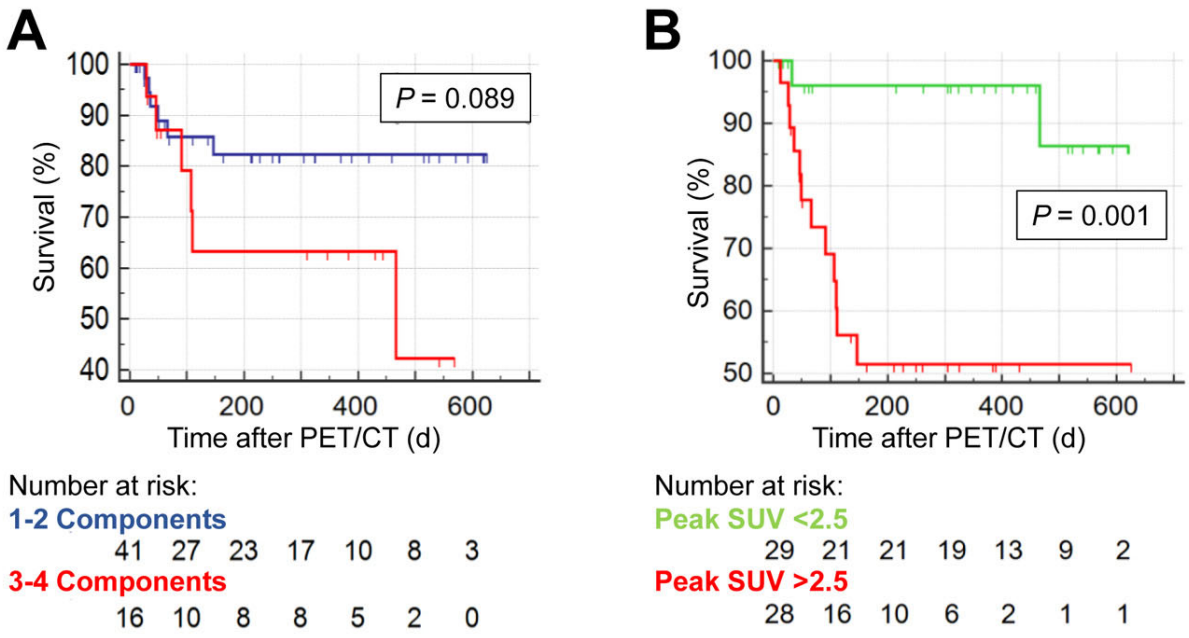

Figure 3: Prognostic value of ^{18}F-fluorodeoxyglucose (FDG) PET/CT in left ventricular assist device (LVAD) infection. Kaplan Meier curves for (A) subgroups of patients with extensive (3-4 LVAD components, red) versus less extensive infection (1-2 components, blue), and (B) patients with thoracic lymph node uptake (peak standardized uptake value, SUV) above (red) versus below median (green).

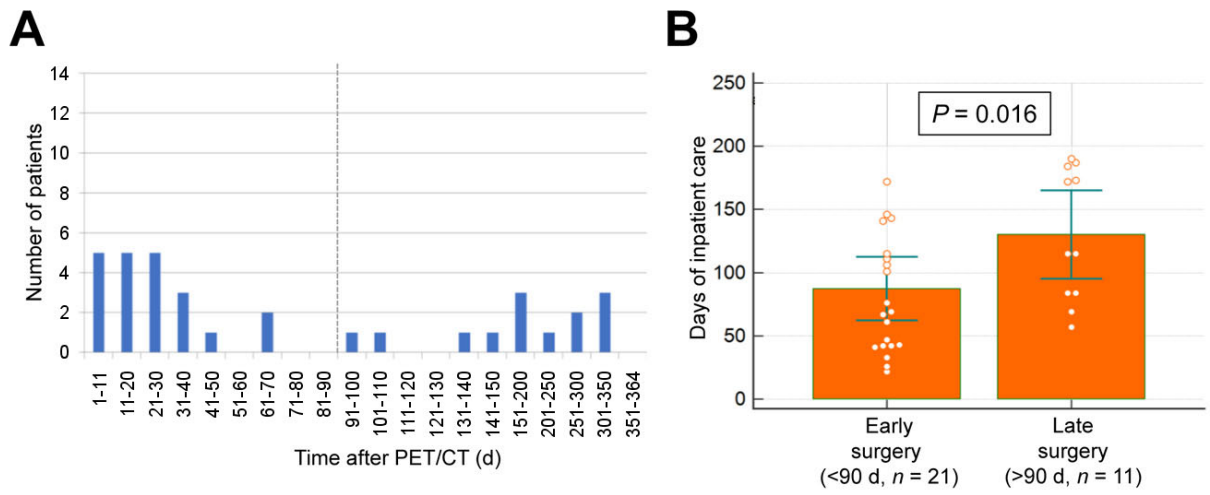

Figure 4: Early surgical revision after ^{18}F-fluorodeoxyglucose (FDG) PET/CT is associated with less inpatient care requirement. (A) Frequency plot for time between PET/CT and subsequent anti-infective surgical procedure. (B) Comparison of inpatient care days in the year after PET/CT in subgroups with early and late surgery.

TABLES

Table 1. Patient characteristics

Clinical parameter	**Value**
Total number of LVAD recipients	57
Age at time of PET (years)	56±11
Gender (female/male; %)	14/86
LVAD carrying time prior to PET (days)	814±708 (48-3273)
Type of LVAD (Heart Mate II/Heart Mate III/Heart Ware/Heart Ware II; %)	24/19/41/16
Underlying type of cardiomyopathy (ischemic/idiopathic dilated/congenital; %)	67/29/4
Antibiotic therapy at the time of PET (%)	88
Type of antibiotic agent (%) - Flucloxacillin / clindamycin - Meropenem - Other (ceftazidime, cefuroxime, unacid, linezolid, vancomycin, gentamycin, cotrimoxazol, piperacillin, ampicillin, daptomycin)	 34 19 47

LVAD, left ventricular assist device; PET, positron emission tomography

Table 2. ^{18}F-FDG uptake at infected LVAD components

Component	**SUV_{max}**	**SUV_{peak}**	**SUV_{mean}**
Driveline entry point (component 1)	7.30 ± 4.44	4.52 ± 2.71	2.57 ± 1.79
Subcutaneous driveline path (component 2)	6.50 ± 4.42	4.24 ± 2.96	2.60 ± 1.79
Pump pocket (component 3)	6.29 ± 3.02	4.19 ± 1.81	2.39 ± 1.11
Outflow tract (component 4)	4.72 ± 2.63	3.45 ± 1.71	2.44 ± 1.25

FDG, ^{18}F-fluorodeoxyglucose; LVAD, left ventricular assist device; SUV, standardized uptake value