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Original article

Left ventricular assist device-related infections: a multicentric study

Running title: Left ventricular assist device-related infections

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ABSTRACT

Objectives. Implantable left ventricular assist device (LVAD) is a major therapeutic progress for end-stage heart failure in selected patients. As their use is expanding, infectious complications are emerging, with limited data available to guide their management. We aimed to better characterize LVAD-related infections.

Methods. We enrolled all consecutive patients diagnosed with LVAD-related infections in 3 referral centers in France, using standardized definition of infections in patients with LVAD. Data were collected from medical charts using a standardized questionnaire.

Results. Between 2007 and 2012, 159 patients received LVAD for end-stage heart failure. Among them, 36 (22.6%) –5 women, 31 men– presented at least one infectious complication, after a median time of 2.9 months from LVAD implantation [interquartile range, 1.8-7.5], with a median follow-up of 12 months [8-17]. Main comorbidities were alcoholism (33%), diabetes (11%) and immunosuppression (11%). Mean age at implantation was 51 (±11) years. LVAD were implanted as bridge-to-transplant (n=22), bridge-to-recovery (n=8), destination therapy (n=4), or unspecified (n=2). LVAD-related infections were restricted to the driveline exit site (n=17), had loco-regional extension (n=13), or reached the internal pump (n=3). The main bacteria isolated were *Staphylococcus aureus* (n=20), coagulase-negative staphylococci (n=7), *Enterobacteriaceae* (n=14), *Pseudomonas aeruginosa* (n=10) and *Corynebacterium* sp. (n=7), with polymicrobial infections in 19 cases. LVAD could be retained in all patients, with the use of prolonged antibacterial treatment in 34 (94%), and debridement in 17 (47%). One patient died due to LVAD-associated infection.

Conclusions. LVAD-related infections are common after LVAD implantation, and may be controlled by prolonged antibiotic treatment.

Introduction

Heart failure is a major cause of morbidity and mortality worldwide [1,2]. The prevalence and incidence of heart failure are increasing [3,4], and the constant shortage of donor organs increases the need for alternatives to heart transplant in patients with end-stage heart failure refractory to medical treatment [5]. Currently, around 2% of the adult population in developed countries suffers from heart failure [6].

In this context, the advent of implantable left ventricular assist device (LVAD) represents a major medical progress for end-stage heart failure in selected patients [7,8], and is currently used as a bridge-to-heart transplantation, a bridge-to-recovery, or as destination therapy (i.e., as the last resort in patients with neither perspectives of recovery, nor heart transplant). Implantable LVAD intended for long-term use rely on a percutaneous driveline, to carry electric signals and energy from the controller and batteries to the implanted pump. As with any other implantable foreign device, LVAD is subject to LVAD-related infections, a consequence of medical progress that is gradually emerging, proportionally to the number of patients implanted with LVAD [9,10]. Indeed, the presence of a driveline piercing the skin places the patient at a continuous risk for infections, that can affect the exit site, the subcutaneous tunnel, the abdominal pocket (if present), the implanted pump, and disseminate through bloodstream infections. The transition from pulsatile to continuous-flow LVAD significantly improved clinical outcome [11], and decreased the risk of infectious complications, but LVAD-related infections are still common [12,13]. Due to the scarcity of data currently available in the medical literature, the management of these emerging infections is poorly standardized, and mostly derives from the state-of-the-art for the management of other cardiovascular devices-related infections (e.g. pacemaker, intra-cardiac defibrillator, prosthetic valves, or vascular prosthesis), although their characteristics are

significantly different. We aimed to better characterize LVAD-related infections, their treatment, and their outcome, through a multi-center study in three referral centers in France.

Methods

La Pitié-Salpêtrière is a 1663-bed university hospital located in Paris (France); Laennec is a 489-bed university hospital located in Nantes (Pays-de-Loire, France); and Pontchaillou is a 992-bed university hospital located in Rennes (Bretagne, France). They all serve as referral centers for end-stage heart failure in their area. Although no national guidelines are currently available for LVAD implantation in France, all three centers use antibacterial prophylaxis with cefamandole for less than 24 hours from the time of LVAD implantation, under rigorous aseptic conditions, with no continuous antibacterial prophylaxis following implantation. Throughout the study period, skin preparation procedures included preoperative shower with chlorhexidine gluconate solution the night before surgery, and two separate skin preparation before incision with either povidone-iodine or chlorhexidine with ethanol in the three participating sites.

Patients with LVAD receive repeated counselling and education by specialized nurse before and after LVAD implantation, to reduce the risk of infection and trauma at the exit site. When LVAD-related complication is suspected, cases are reviewed by the endocarditis team in each site, including at least one cardiac surgeon, one infectious diseases specialist, and one microbiologist. In the absence of any consensus on the management of LVAD-related infections during the study period, patients were managed on a case-by-case basis, taking into account clinical and microbiological data, including drug susceptibility profiles. Follow-up was tailored to the characteristics of LVAD-related complications, and was mostly performed by the cardiac surgery department, in association with infectious diseases

specialist for any suspicion of infectious complication. All patients enrolled in these databases provided informed consent for observational studies.

Cases of LVAD-related infections were identified through a retrospective review of medical charts for all patients with LVAD implanted from January 2007 to December 2012 in the participating centers. LVAD-related infections were defined according to criteria established by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [14], the North American registry for mechanical circulatory support devices (MCSD) that serves as a quality improvement system to assess the characteristics, treatments, and outcomes of patients receiving MCSD. Briefly, percutaneous site infections were defined as pain, erythema, or purulent drainage restricted to the LVAD entry site, with a positive culture from the skin, and the decision to initiate systemic antimicrobial therapy. LVAD-related infections were defined as loco-regional when the erythema or induration extended >1 cm along the subcutaneous part of the driveline, and/or in case of fever or leukocytosis not explained by other conditions, with the decision to initiate systemic antimicrobial therapy. Lastly, LVAD-related infections where classified as pump infections when an indistinguishable organism (genus, species, and antimicrobial susceptibility pattern) was recovered from 2 or more peripheral blood cultures taken at least 12 hours apart with no other focus of infection, leading to the initiation of an antimicrobial treatment.

A standardized questionnaire was used to collect demographical, clinical, and laboratory data from medical records, with a focus on the clinical features and microbiology of LVAD-related infections, any surgical and antibacterial treatment, and outcome. Statistical analyses were descriptive. Categorical variables were presented as number and percentages. Continuous variables were presented as either means with standard deviations (SD), or medians with first- and third-quartile [interquartile range, IQR], if the distribution of the data

were skewed. Statistical analyses were performed using STATA software, version 12 (STATA Corporation).

Results

Between January 2007 and December 2012, 159 patients underwent LVAD implantation at La Pitié-Salpêtrière, Paris (n=103), Laennec, Nantes (n=32), and Pontchaillou, Rennes (n=24). Of these, 36 patients (22.6%) presented at least one LVAD-related infection during the study period, with a median follow-up of 12 months [IQR, 8-17]. Patients characteristics and features of LVAD-related infections are presented in tables 1 and 2. The median delay from LVAD implantation to the diagnosis of LVAD-related infection was 2.9 months [1.8-7.5]. Microbiology documentation of LVAD-related infections was obtained using swabs taken from the entry site (56%), surgical samples during debridement (20%) or during heart transplant (7%), blood culture (10%), and transcutaneous puncture (3%). Infections were polymicrobial in 54% of cases. Main pathogens were *Staphyloccocus aureus* (n=20, including 2 meticillin-resistant), *Enterobacteriaceae* (n=12, including 7 extended spectrum beta-lactamase producers), *Pseudomonas aeruginosa* (n=10), coagulase-negative staphylococci (n=6, including 2 meticillin-resistant), *Corynebacterium* sp. (n=6), and others (*Acinetobacter baumanii*, *Haemophilus aprophilus*, and *Stenotrophomonas malthophilia*, one patient each).

LVAD-related infections required hospital admission in 28 cases (78%). All patients received systemic antibacterial treatment, based on pathogen(s) identification and drug susceptibility testing. Antibacterial treatment was temporarily administered by the intravenous route in 27 patients (75%), while 9 patients only received oral antibiotics. The median total duration of antibacterial treatment for LVAD-related infections was 90 days [40-

120] per patient. Surgical debridement and drainage were performed in 17 patients (47%). Indications for surgery were either loco-regional infection associated with collection documented by computed tomography scanning or ultrasound (n=12), or pump infection (n=5). Procedures were always implemented with concomitant antibacterial treatment. Three of the 17 patients treated with debridement required a second local surgery due to persistent drainage on appropriate antibacterial treatment. No patient required wound vacuum-assisted-closure (VAC), pump relocation, or antibiotic beads at the device pocket.

The outcome was satisfactory in most cases: LVAD was finally extracted because of heart transplant (n=17) - with a median time to transplantation of 11.3 months [8.9-15.0], or because of recovery from heart failure (n=4). No patient underwent LVAD extraction because of uncontrolled infection, and no LVAD-related infection was considered as a definitive contra-indication for heart transplant. During the study period, 3 patients died, of whom one was considered as attributable to LVAD-related infection. Of the 12 patients with the LVAD still in place by the time of last follow-up, three had stopped all antibacterial treatment - with a follow-up of 52, 98, and 138 days since last antibacterial treatment - and nine were on prolonged oral antibacterial treatment. Most patients (n=34, 94%) presented no sequel of their LVAD-related infection.

Discussion

The most salient features of this multi-center study of LVAD-related infections performed in three referral centers are as follows: Firstly, we confirmed that infectious complications are very common early after LVAD implantation, documented in almost one quarter of patients, with a median follow-up of one year. This is in agreement with previous

series, and not unexpected given the continuous percutaneous portal of entry, and the comorbidities presented by these patients with end-stage heart failure. Secondly, we provided a comprehensive documentation of the major pathogens involved in this emerging foreign device-related infectious diseases, where the 'big five' are – as could be expected – *S. aureus*, *Enterobacteriaceae*, *P. aeruginosa*, coagulase-negative staphylococci, and *Corynebacterium* sp. Thirdly, we found that, despite the major challenges arising when infections occur on a life-saving device, the overall outcome was favorable in most instances, at the price of prolonged systemic antibacterial treatment for > 90% of patients, and surgical debridement for almost half of them. This satisfactory outcome may be related to the destiny of these devices, mostly implanted as bridge-to-transplantation, or bridge-to-recovery: Indeed, in this situation, the main challenge for the management of LVAD-related infections is to keep the device in place until it is no longer necessary, which is not the case for other foreign device-related infections, such as prosthetic valve, vascular prosthesis, or prosthetic joints, usually planned to remain in place lifelong.

To our knowledge, few studies have reported the incidence, the characteristics, and the management of LVAD-related infections thus far. Previous reports found an incidence of LVAD-related infections similar to our cohort, but with a median time from LVAD implantation that was slightly longer, at 4.4 to 7.4 months [13,15], as compared to 2.9 months in our study. These discrepancies may be related to the close monitoring routinely implemented after LVAD implantation in our centers, to limited sample size, or to the fact that 58% of our patients were classified as INTERMACS I by the time of implantation, which has been associated with earlier first pump-related infection [16]. Microbiological characteristics of previous series are remarkably similar to ours, although one previous series also isolated fungi as potentially involved (17). Of note, 22 isolates were Gram negative bacilli in our series, including 19 non-susceptible to the antibioprophylactic regimen routinely

used during LVAD implantation in our sites (i.e. cefamandole): extended spectrum beta-lactamase producing *Enterobacteriaceae* (n=7), and non-fermeting Gram negative bacilli (n=12). However, given the median delay from LVAD implantation to infection diagnosis (2.9 months), this is unlikely that an antibiopropylactic regimen with broader coverage would have prevented these infections. We found that percutaneous driveline exit is the most common site of LVAD-related infections, as in previous reports. Given that a number of studies have demonstrated that trauma at the exit site favors the development of driveline infections [10,18], prevention of driveline trauma may decrease the risk of LVAD-related infections. Hence, patient education is an important component for the prevention of LVAD-related infections, and goes behind hygiene and infection control education.

Up to now, the management of LVAD-related infections is poorly standardized, due to the scarcity of therapeutic studies in the field, and the absence of consensus guidelines. To assist therapeutic decisions in this challenging context, Koval et al proposed recommendations based on observational studies and experts opinion [18]. The management of LVAD-related infections in our center follows the main principles depicted in these recommendations, including anti-infectious treatment adapted to microbiology in all cases, with surgical revision in selected cases. Although LVAD exchange is an option, this high-risk surgery is often contra-indicated, and the use of continuous or iterative course of antibiotics until transplantation, or recovery, is the rule for most centers.

Our study has limitations. First, although data were prospectively collected, the original database did not focus on infectious complications. Hence, collection of clinical data and microbiological investigations were not standardized. To address this limitation, the three participating sites have implemented a prospective database for all patients who receive LVAD since January 2012, with systematic follow-up at the referral center at one month and three months after implantation, and then at least every 6 months, as well as each time

requested by the patient and/or his general practitioner. Second, due to limited sample size, and the participation of three centers with similar practices in a restricted geographic area, our findings may not apply to other sites with different practices, different case mix, or different bacterial epidemiology. Third, the management of LVAD-related infections was not standardized during the study period. Indeed, patients were managed on a case-by-case basis, by the local endocarditis team. This could have led to heterogeneity from one site to another, although endocarditis teams follow the same basic principles, have access to similar diagnostic tools and anti-infective treatment, and prioritize evidence-based medicine when available.

Conclusions

LVAD is a significant progress that improves survival status, functional capacity, and quality of life, but it carries a high risk of infectious complications, evaluated at 22.6% at one year in this study. With systemic antibacterial treatment for all patients, and debridement in selected cases, the final outcome is usually satisfactory, as most cases of LVAD-related infections may be controlled, with no sequel, and no contraindication for heart transplant.

Transparency declaration and financial support statement

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Table 1. Characteristics of patients with left ventricular assist device-related infections (n=36) by time of implantation

Variables	
Demographic characteristics	
Age at implantation (years)	51 ± 11
Male	31 (86)
Comorbidity	
Immunocompromised	4 (11)
Diabetes mellitus	4 (11)
Chronic alcoholism	12 (33)
Left ventricular ejection fraction (%)	22 ± 7
Body mass index (kg/m^2)	25.4 ± 4.9
Aetiology of heart failure	
Ischemic cardiomyopathy	22 (61)
Dilated cardiomyopathy	14 (39)
Duration of heart failure	
< 12 months	17 (48)
1-5 years	9 (26)
> 5 years	9 (26)
Indication of LVAD implantation [a]	
Bridge-to-transplantation	22 (65)
Bridge-to-recovery	8 (23)
Destination therapy	4 (12)
INTERMACS profile [b]	
I	21 (58)
II	0 (0)
III	5 (14)
IV	3 (8)
V-VII	7 (20)
LVAD device	
Heartmate II (Thoratec)	33 (92)
Others [c]	3 (8)

Categorical data are summarized as Number (%) of patients and continuous data are summarized as mean ± standard deviation.

LVAD, left ventricular assist device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support

[a] Data available for 34 patients; [b], INTERMACS profile I = critical cardiogenic shock, II = progressive decline on inotropic support, III = stable, but inotrope dependent, IV = resting symptoms, V = exertion intolerant, VI = exertion limited, VII = adavanced New York heart association class 3; [c] Heartware, Thoratec (n=2); VentrAssist, Ventracor (n=1)

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Table 2

Characteristics and management of left ventricular assist device-associated infections (n=36)

Variables	
Clinical manifestation	
Time from implantation to infection, months	2.9 [1.8-7.5]
Purulent drainage	31 (86%)
Pain	17 (47%)
Erythema	22 (61%)
Fever	28 (80%)
Infection site [a]	
Percutaneous driveline	17 (49%)
Locoregional	13 (37%)
Pump	5 (14%)
Laboratory variables	
White Blood Cell count, 10^9/L	11.8 [5.6-27.7]
Serum C Reactive Protein, mg/l	26 [3-362]
Positive blood culture(s)	4 (10%)
Microbiology	
Staphylococcus aureus	20 (56%) [b]
Enterobacteriaceae	12 (33%) [c]
Pseudomonas aeruginosa	10 (28%)
Coagulase-negative staphylococci	6 (18%)
Corynebacterium sp.	6 (18%)
Others	3 (8%) [d]
Management	
Systemic antibacterial treatment [e]	36 (100%)
Median duration (days)	40 [14-120]
Surgical debridement	17 (47%)

Categorical data are summarized as Number (%) of patients and continuous data are summarized as median values [first quartile-third quartile].

[a] data available for 35 patients

[b] including 2 (10%) methicillin-resistant *Staphylococcus aureus*

[c] including 7 (58%) extended spectrum beta-lactamase producers

[d] *Acinetobacter baumanii*, *Haemophilus aprophilus*, and *Stenotrophomonas malthophilia*, one patient each

[e] Antibacterial treatment included cloxacillin (n=21), pristinamycin (n=15), ciprofloxacin (n=12), gentamicin (n=12), amikacin (n=9), vancomycin (n=7), imipenem (n=7), rifampin (n=6), piperacillin-tazobactam (n=5), and ofloxacin, amoxicillin-clavulanate, amoxicillin, trimethoprime-sulfamethoxazole, clindamycin, doxycyclin, fusidic acid, ceftazidime, ceftriaxone, cefamandole, and linezolid (n<5 for each).