Risk factors and prognostic impact of left ventricular assist device–associated infections

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Background Left ventricular assist device (LVAD)–associated infections may be life-threatening and impact patients' outcome. We aimed to identify the characteristics, risk factors, and prognosis of LVAD-associated infections.

Methods Patients included in the ASSIST-ICD study (19 centers) were enrolled. The main outcome was the occurrence of LVAD-associated infection (driveline infection, pocket infection, or pump/cannula infection) during follow-up.

Results Of the 652 patients enrolled, 201 (30.1%) presented a total of 248 LVAD infections diagnosed 6.5 months after implantation, including 171 (26.2%), 51 (7.8%), and 26 (4.0%) percutaneous driveline infection, pocket infection, or pump/cannula infection, respectively. Patients with infections were aged 58.7 years, and most received HeartMate II (82.1%) or HeartWare (13.4%). Most patients (62%) had implantable cardioverter-defibrillators (ICDs) before LVAD, and 104 (16.0%) had ICD implantation, extraction, or replacement after the LVAD surgery. Main pathogens found among the 248 infections were *Staphylococcus aureus* (n = 113' 45.4%), *Enterobacteriaceae* (n = 61; 24.6%), *Pseudomonas aeruginosa* (n = 34; 13.7%), coagulase-negative staphylococci (n = 13; 5.2%), and *Candida* species (n = 13; 5.2%). In multivariable analysis, HeartMate II (subhazard ratio, 1.56; 95% CI, 1.03 to 2.36; *P* = .031) and ICD-related procedures post-LVAD (subhazard ratio, 1.43; 95% CI, 1.03-1.98; *P* = .031) were significantly associated with LVAD infections. Infections had no detrimental impact on survival.

Conclusions Left ventricular assist device–associated infections affect one-third of LVAD recipients, mostly related to skin pathogens and gram-negative bacilli, with increased risk with HeartMate II as compared with HeartWare, and in patients who required ICD-related procedures post-LVAD. This is a plea to better select patients needing ICD implantation/replacement after LVAD implantation. (Am Heart J 2019;214:69-76.)

Heart failure is a major cause of morbidity and mortality worldwide: around 2% of the adult population in developed countries have heart failure.[1] Its prevalence and incidence are increasing, 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.[2]

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In this context, the advent of implantable left ventricular assist device (LVAD) represents a major medical progress[3,4] and is currently used as a bridge-to-heart transplantation, as bridge-to-recovery, or as a long-term myocardial surrogate, termed as *destination therapy*.[5] Implantable LVAD intended for long-term use relies on a percutaneous driveline, to carry electric energy from the batteries to the implanted pump. As with any other implantable foreign device, LVAD is subject to LVAD-associated infections, whose incidence is constantly growing, proportionally to the number of patients implanted with LVAD.[6-8] Indeed, the presence of a driveline piercing the skin places the patient at a continuous risk for infections, which 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 outcomes[9] and decreased the risk of infectious complications, but LVAD-associated infections are still common.[10-13]

Because of 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 management of other cardiovascular device-related infections (eg, pacemaker, implantable cardioverter-defibrillator [ICD], prosthetic valves, or vascular prosthesis), although their characteristics are significantly different. Thus, we aimed to describe LVAD-associated infections and their risk factors and prognosis through a large-scale multicenter retrospective observational study of patients implanted with LVAD.

Methods

Study population

This study was a retrospective analysis of the multicenter observational ASSIST-ICD study ("Determination of Risk Factors of Ventricular Arrhythmias After Implantation of Continuous Flow Left Ventricular Assist Device" ClinicalTrials.gov NCT02873169), including 19 tertiary centers. The methods of this study were previously published.[14] Briefly, patients aged ≥18 years who had been implanted with axial HeartMate 2 (Abbott, Chicago, IL), Jarvik2000 (Jarvik Heart, Inc, New York, NY), or centrifugal HeartWare pumps (Medtronic, Columbia Heights, MN) between February 2006 and December 2016 were included. Exclusion criteria were patients who underwent total artificial heart placement or pulsatile flow LVAD and VentrAssist (Ventracor, Chatswood, NSW, Australia) recipients. This study was entirely funded by the French Federation of Cardiology using a grant obtained by the principal investigators. Of note, the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

This study was approved by the regional ethic committees, the French Advisory Committee on the Treatment of Research Information in the Field of Health, and the French National Commission of Informatics and Civil Liberties. A nonopposition letter was sent to patients, as requested by French authorities for retrospective studies.

LVAD implantation procedure and follow-up

Although no national guidelines were available for LVAD implantation in France during the study period, most centers used cefamandole as first-line prophylaxis for less than 24 hours from the time of LVAD implantation, under rigorous aseptic conditions, with no continuous antibacterial prophylaxis after implantation. Throughout the study period, skin preparation procedures included preoperative shower with chlorhexidine gluconate solution the night before surgery and 2 separate skin preparation before incision with either povidone-iodine or chlorhexidine with ethanol. Patients with LVAD received repeated counseling and education by specialized staff before and after LVAD implantation, to reduce the risk of infection and trauma at the exit site. Patients were followed up in their referral centers depending on local habits: mainly monthly the first year, then every 3 to 6 months. In addition, they could be attended whenever deemed necessary. When an LVAD-associated infection was suspected, cases were reviewed by the endocarditis team in each site, including at least 1 cardiac surgeon, 1 infectious diseases specialist, and 1 microbiologist.

Definitions of LVAD-associated infections

We focused on LVAD-specific infections, as defined by the International Society for Heart and Lung Transplantation criteria, that is, infections that are related to the device hardware: percutaneous driveline infections, pocket infections, and/or pump/cannula infections.[15] Briefly, (1) percutaneous driveline 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; (2) pocket infections were defined by the combination of 2 major criteria: (i) new fluid collection surrounding the pocket identified by radiologic criteria (computed tomographic enhancement/ultrasound and/or gas or sinus tract) and (ii) fluid culture positive, or by the combination of 1 major criterion (see above) and 3 minor criteria, as follows: (i) fever ≥38°C with no other recognized cause, (ii) new local erythema over the pocket site, (iii) local pain and tenderness, (iv) induration or swelling, and (v) radiologic evidence not fulfilling major criteria; and (3) lastly, pump/cannula infections were defined by a combination of 2 major criteria, derived from modified Duke criteria: (i) 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 and (ii) echocardiogram findings of intracardiac mass suspected to be vegetation adjacent to or in the outflow cannula, or in an area of turbulent flow, or on implanted material, or abscess, or new partial dehiscence of outflow cannula, or by the combination of 1 major and 3 minor criteria, as follows: (i) fever ≥38°C with no other recognized cause; (ii) vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, conjunctival hemorrhage, and Janeway lesions; (iii) immunologic phenomena, such as glomerulonephritis, Osler nodes, and Roth spot; and (iv) microbiologic evidence not fulfilling major criteria.

Statistical analysis

Categorical variables were presented as number and percentages. Continuous variables were presented as medians with first and third quartiles (interquartile range, or IQR). Qualitative data were compared using χ^2 or Fisher exact tests, while quantitative data were compared using Mann-Whitney test. All tests were 2-sided at the .05 significance level. Overall and free from LVAD-associated infections survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. All univariable analyses were performed on complete cases. Predictors of LVAD-associated infections were analyzed using univariable and multivariable Fine and Gray Cox models accounting for death and heart transplant as competing events. Variables with $P < .1$ in univariable analysis and age at implantation were included in the multivariable analysis. Results are expressed as subhazard ratio (sHR) with their respective 95% CI. The impact of LVAD-associated infections on survival was analyzed using univariable and multivariable Cox models. There were no missing data among the 7 variables with $P < .1$ in univariable analysis included in the multivariable analysis. For the purposes of the multivariable analysis, missing data were handled by multiple imputations using the Markov Chain Monte Carlo method, assuming that they were missing completely at random. Ten imputed data sets were created; results were pooled according to Rubin's rule and reported as adjusted HR with their 95% CI. Statistical analyses were conducted using the Statistical Package for Social Sciences version 22 (SPSS Inc, IBM, Armonk, NY) and Stata Statistical Software release 13 (StataCorp, LLC, College Station, TX).

Results

Patients' characteristics

Between February 2006 and December 2016, 659 patients were implanted with a continuous-flow LVAD. Among these, 7 patients were excluded (3 patients received a VentrAssist and 4 patients died during the LVAD surgery). Hence, 652 patients were included in the final analysis. Patients' characteristics are presented in Table I. Among these patients, 561 (86%) were men, with a median age of 59.8 years (51.4-66.4 years) at the time of LVAD implantation.

LVAD-associated infections

Of the 652 patients enrolled, 201 (30%) presented a total of 248 LVAD-associated infections during the study period, including 171 (26%), 51 (8%), and 26 (4%) percutaneous driveline infection, pocket infection, or pump/cannula infection, respectively (patients could have >1 infection). The median delay from LVAD implantation to the first diagnosed LVAD-associated infection was 6.5 months (3.1-12.4). The estimated survival rates without LVAD-associated infections at 1, 2, and 3 years were 65.7% (95% CI, 60.8%-70.1%), 53.5% (95% CI, 47.8%-58.9%), and 41.4% (95% CI, 34.6%-48.1%), respectively. The survival free from driveline, pocket, or pump/cannula infection is shown in Figure 1A.

As described in Table I, patients with or without infections during follow-up had similar clinical characteristics and comorbidities. However, a significant difference in terms of type of LVAD implanted was observed (82% and 69% of HeartMate II, respectively). Furthermore, the LVAD indication significantly differed among groups. Most patients (n = 403; 62%) had an ICD implanted before LVAD, and 104 (16%) underwent ICD-related procedures after the LVAD surgery (extraction, replacement, or implantation for those not having an ICD at the time of LVAD surgery).

Among the 248 LVAD-associated infections, the main pathogens involved were *Staphylococcus aureus* (n = 113), *Enterobacteriaceae* (n = 61), *Pseudomonas aeruginosa* (n = 34), coagulase-negative staphylococci (n = 13), and *Candida* species (n = 13; some patients had ≥2 germs). Main characteristics of LVAD-associated infections involving the driveline exit site, the pocket, and/or the pump/cannula are presented in Table III. As shown in Figure 1B, the time from LVAD implantation to infection varied depending on the pathogen, from 1.7 (IQR, 0.9-6.8) to 9.9 (5.3-17.6) months for *Candida* species and *Enterobacteriaceae*, respectively ($P = .014$).

Predictors of LVAD-associated infections

In competing risk regression accounting for death, heart transplant, hypertension ($P = .045$), intra-aortic balloon pump before LVAD ($P = .03$), HeartMate II ($P = .016$), destination therapy ($P = .006$), and ICD-related procedures post-LVAD ($P = .003$), were associated with LVAD-associated infections. On multivariable analysis (Table II), only HeartMate II (sHR, 1.56; 95% CI, 1.03-2.36; $P = .037$) and ICD-related procedures post-LVAD (sHR, 1.43; 95% CI, 1.03-1.98; $P = .031$) were independently associated with LVAD-associated infections. Interestingly, as shown in Table IV, the type of pathogens responsible for LVAD-associated infections in patients with or without ICD-related procedures was

Table I. Patients characteristics

	All patients (n = 652)	Patients with LVAD-associated infection (n = 201)	Patients without LVAD-associated infection (n = 451)	*P*
Age (y), median (IQR)	59.8 (51.4-66.4)	58.7 (50.9-65.1]	60.3 (51.8-67.0]	.056
Men (%)	561 (86)	171 (85)	390 (86)	.723
Body mass index (kg/m^2), median (IQR)	25.3 (22.6-27.8)	25.1 (22.8-28.1)	25.3 (22.6-27.8)	.949
Hypertension (%)	233 (36)	61 (30)	172 (38)	.068
Diabetes mellitus (%)	154 (24)	43 (21)	111 (25)	.427
Dyslipidemia (%)	283 (43)	83 (41)	200 (44)	.488
History of smoking (%)	395 (61)	120 (60)	275 (61)	.825
Heart failure etiology (%)				.522
Ischemic	412 (63)	124 (62)	288 (64)	
Idiopathic	178 (27)	57 (28)	121 (27)	
Other	62 (13)	20 (10.0)	42 (9)	
Heart failure duration (mo), median (IQR)[a]	61 (2-169)	48 (1-135)	68 (2-179)	.059
History of supraventricular arrhythmias (%)[a]	302 (46)	97 (48)	205 (45)	.563
LVEDD (mm), median (IQR)[a]	70 (64-75)	70 (63-76)	69 (64-75)	.740
LVEF (%), median (IQR)[a]	20.0 (15-25)	20 (15-25)	20 (15-25)	.534
ICD (%)[a]	403 (62)	121 (60)	282 (63)	.595
Cardiac resynchronization therapy (%)[a]	198 (30)	60 (30)	138 (31)	.921
Biology serum				
Creatinine (μmol/L)	115.0 (87.0-148.0)	119.7 (84.5-146.0)	112.5 (88.0-149.0)	.860
Serum sodium (mmol/L)	136.0 (132.0-139.0)	135.0 (132.0-139.0)	136.0 (132.0-139.0)	.379
Total bilirubin (mmol/L)	16.0 (10.0-27.0)	15.0 (10.0-24.0)	16.0 (10.6-27.3)	.222
Temporary mechanical support (%)	258 (40)	84 (42)	174 (38)	.492
ECLS	136 (21)	42 (21)	94 (21)	.929
Intra-aortic balloon pump	58 (9)	26 (13)	32 (7)	**.023**
Impella	64 (10)	16 (8)	48 (11)	.357
Type of LVAD (%)				
HeartMate II	475 (73)	165 (82)	310 (69)	**.002**
HeartWare	127 (19)	27 (13)	100 (22)	
Jarvik2000	50 (8)	9 (4)	41 (9)	
LVAD indication (%)				
Bridge-to-transplantation	387 (59)	137 (68)	250 (55)	**.009**
Destination therapy	247 (38)	60 (30)	187 (41)	
Bridge-to-decision/recovery	18 (3)	4 (2)	14 (3)	
Combined surgery with LVAD (%)	95 (15)	31 (15)	64 (14)	.771
Right ECLS during surgery (%)	81 (12)	21 (10)	60 (13)	.372
Patients with ICD-related procedures post-LVAD (%)	104 (16)	47 (23)	57 (12)	<**.001**

Categorical variables are presented as number (%). Continuous variables are presented as medians (IQR).
Abbreviations: *ECLS*, Extracorporeal life support; *ICU*, intensive care unit; *LVEDD*, left ventricular end-diastolic diameter; *LVEF*, left ventricular ejection fraction.
a Before LVAD implantation

different, because the proportion of *S aureus* and *P aeruginosa* significantly differed (68% vs 41% [*P* = .002] and 4% vs 18% [*P* = .035], respectively).

Impact of LVAD-associated infections on survival

Among the 652 patients analyzed, 22 (3%) had an infection during the in-hospital stay after LVAD implantation, including 14 driveline, 7 pocket, and 5 pump/cannula infections. Eight of these infected patients died during this index hospitalization, including 4 who died of a septic shock. A total of 494 patients were discharged alive from the hospital. Among them, 179 (36%) had an infection, including 157 driveline, 44 pocket, and 21 pump/cannula infections. Fifty-one of these infected patients eventually died, including 14 who died of a septic shock. Death occurred 4.4 (1.7-9.8) months after the infection was diagnosed. In summary, 18 patients (10%) died of a septic shock during follow-up.

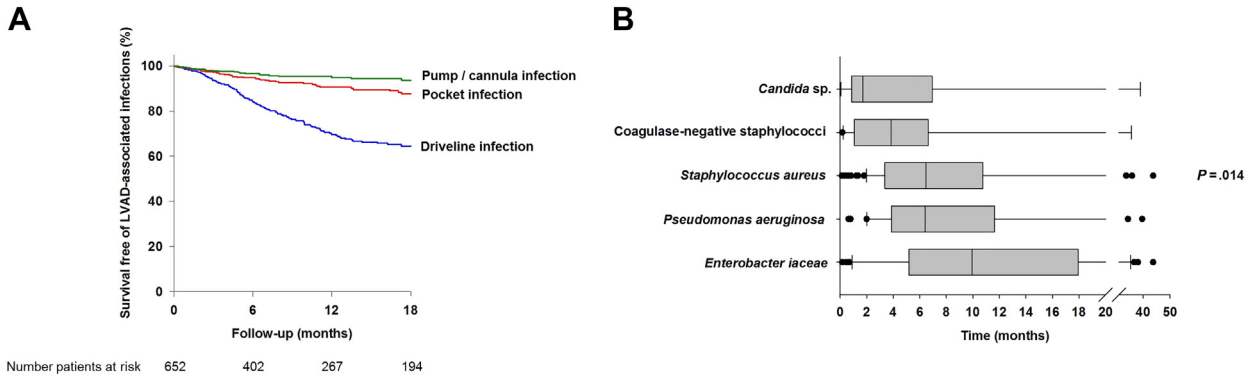
After adjustment for other variables associated with survival in univariate analysis, LVAD-associated infections had no detrimental impact on long-term survival (HR. 0.54; 95% CI, 0.39-0.73; *P* < .001). Patients who had LVAD-associated infections more often underwent heart transplant (42% vs 26%, *P* < .001).

Discussion

Main results

The main results of this multicenter study of LVAD-associated infections performed in 19 referral centers are as follows: (1) first, we confirmed that infectious complications are common after LVAD implantation, documented in 30% of patients, with a median duration

Figure 1



A, Survival free from driveline, pocket, or pump/cannula infection. The estimated survival rates at 12 months without driveline, pocket, and pump/cannula infections were 69.7% (64.8-74.1), 90.5% (87.0-93.1), and 95.4% (92.8-97.0), respectively. **B**, Time from LVAD implantation to infection for the main pathogens.

Table II. Univariate and multivariate analyses of risk factors for LVAD-associated infections

Variables	Univariate sHR (95% CI)	*P*	Multivariable sHR (95% CI)	*P*
Age at implantation, per 1-y increase	0.99 (0.98-1.00)	.25	1.01 (0.99-1.02)	.34
Hypertension	0.74 (0.55-0.99)	.045	0.79 (0.58-1.06)	.12
Heart failure duration before LVAD, per 1-mo increase	0.999 (0.998-1.000)	.076	0.999 (0.998-1.001)	.34
IABP before LVAD implantation	1.57 (1.04-2.35)	.03	1.27 (0.81-1.99)	.30
Type of LVAD				
HeartMate II (vs HeartWare)	1.67 (1.10-2.53)	.016	1.56 (1.03-2.36)	.037
Jarvik 2000 (vs HeartWare)	0.86 (0.40-1.88)	.71	0.97 (0.43-2.17)	.93
LVAD indication				
Destination therapy (vs bridge-to-transplantation)	0.65 (0.48-0.88)	.006	0.70 (0.49-1.01)	.056
Bridge-to-recovery/decision (vs bridge-to-transplantation)	0.59 (0.23-1.53)	.28	0.55 (0.22-1.34)	.19
ICD-related procedures post-LVAD	1.59 (1.17-2.16)	.003	1.43 (1.03-1.98)	.031

Abbreviation: *IABP*, Intra-aortic balloon pump.

of 6.5 months between LVAD implantation and first infectious complication. 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. (2) Second, we provided a comprehensive documentation of the major pathogens involved in these emerging foreign device–associated infectious diseases, where the major players are *S aureus*, *Enterobacteriaceae*, *P. aeruginosa*, coagulase-negative staphylococci, and *Candida* species. (3) Third, we found that only HeartMate II (sHR, 1.56; 95% CI, 1.03-2.36; $P = .037$) and ICD-related procedures post-LVAD (sHR, 1.43; 95% CI, 1.03-1.98; $P = .031$) independently predicted the risk of LVAD-associated infections.

Microbiology of LVAD-associated infections

To our knowledge, few studies have reported the incidence, characteristics, and risk factors for LVAD-associated infections thus far. Previous reports found similar incidence of LVAD-associated infections, with a large predominance of driveline infections and a median duration between LVAD implantation and infection diagnosis ranging from 2.9 to 7.4 months.[3,5,6,9-11,16-28] Microbiological characteristics of previous series are remarkably similar to ours, with a predominance of staphylococci, *Pseudomonas* species, and *Enterobacteriaceae*.[16,25,27] Of note, most gram-negative bacilli responsible for LVAD-associated infections are nonsusceptible to the antibioprophylactic regimen routinely used during LVAD implantation in our sites (ie, cefamandole, a second-generation cephalosporin). However, given the median delay from LVAD implantation to infection diagnosis (>2 months in all series published thus far), this is unlikely that a perioperative antibioprophylactic regimen with broader coverage would prevent these infections.

Predictors of LVAD-associated infections

We found that only HeartMate II (vs HeartWare) and ICD-related procedures post-LVAD implantation (ICD

Table III. Characteristics of LVAD-associated infectionsa, b

	Total LVAD-associated infection (any site; n = 201)	Percutaneous driveline infection (n = 171)	Pocket infection (n = 51)	Pump/cannula infection (n = 26)	*P*
Time from LVAD implantation to infection (mo), median (IQR)	6.5 (3.1-12.4)	6.9 (3.9-13.0)	6.2 (2.3-13.5)	4.6 (1.3-8.0)	.056
Pathogens (%)[a,b]					
S aureus	113 (56)	85 (50)	20 (39)	8 (31)	.116
Enterobacteriaceae	61 (30)	45 (26)	12 (23)	4 (15)	.474
P aeruginosa	34 (17)	26 (15)	5 (10)	3 (11)	.581
Coagulase-negative staphylococci	13 (6)	9 (5)	4 (8)	0	.344
Candida species	13 (6)	3 (2)	5 (10)	5 (19)	**<.001**

Categorical variables are presented as number (%). Continuous variables are presented as medians (IQR).
a Patients could have more than one.
b Some cases had no microbiological documentation.

Table IV. Type of pathogens involved in LVAD-associated infections in patients with and without ICD-related procedures

	ICD-related procedure post-LVAD (n = 47)	No ICD-related procedure post-LVAD (n = 154)	*P*
S aureus (%)	32 (68)	63 (41)	.002
Enterobacteriaceae (%)	13 (28)	32 (21)	.429
P aeruginosa (%)	2 (4)	28 (18)	.035
Coagulase-negative staphylococci (%)	1 (2)	13 (8)	.256
Candida species (%)	0 (0)	9 (6)	.203

implantation, extraction, or replacement) were independent predictors of LVAD-specific infections. HeartMate II is a second-generation LVAD, with an extracardiac continuous-flow rotary pump, whereas HeartWare is a third-generation centrifugal LVAD with a smaller pump, placed in the pericardial space. Although the advent of third-generation LVAD aimed at reducing the risk of complications, this is the first time that HeartWare is independently associated with a reduced risk of infectious complications, as compared with HeartMate II, in a large clinical study. Stulak et al[11] found no difference in the incidence of LVAD-associated infections between the 2 devices, but patients implanted with HeartMate II (n = 560) were more often receiving destination therapy, had a lower preoperative creatinine level, and had less preoperative right ventricular dysfunction compared with patients implanted with HeartWare (n = 174) in that study. Conversely, in the ENDURANCE trial, patients implanted with HeartWare experienced numerically more driveline exit site infection and significantly higher rate of sepsis compared with those receiving HeatMate 2 (19.6% vs 15.4% [*P* = .30] and 23.6% vs 15.4% [*P* = .048], respectively).[29] Risk factors for LVAD-associated infections after continuous LVAD implantation in previous studies included age, revision for bleeding, duration of intensive care unit stay,[6] obesity,[30] history of depression, baseline serum creatinine,[20] tunnel technique during LVAD implantation,[23] dressing technique postimplantation,[31] and percutaneous driveline traumatism.[18,31]

Interestingly, we found that ICD-related procedures post-LVAD, including ICD implantation, extraction, or replacement, is associated with a 43% increase in LVAD-associated infections. This parameter has never been identified as an independent risk factor for infection,[17] although being biologically plausible. This is a plea to better select patients needing ICD implantation or replacement after LVAD implantation, that is, those at risk of late ventricular arrhythmias after LVAD implantation. We recently reported that the so-called VT-LVAD score,[14] which provided external validation, could have the potential to precisely assess the risk of arrhythmias of LVAD recipients, thus discriminating patients at low, intermediate, high- and very high risk of ventricular arrhythmias. Implantable cardioverter-defibrillator interventions could be avoided in low-risk patients (no ICD implantation/replacement) and carefully discussed for those with intermediate risk. In the light of the results of the present study, those patients with an expected high risk of ventricular arrhythmias should have ICD interventions before LVAD implantation, if required interventions can be anticipated, to avoid subsequent LVAD infections. Nevertheless, physicians should stay alert to clinical and biological signs of LVAD infections for those patients requiring ICD interventions after LVAD surgery.

Interestingly, contrarily to what one may think, the use of a temporary mechanical support (extracorporeal life support, intra-aortic balloon pump, or Impella) before LVAD implantation was not a predictor of LVAD-associated infection.

Impact of LVAD-associated infections on survival

In our study, 10.1% of infected patients died of septic shock. However, overall, LVAD-associated infections did not negatively impact patients' survival. Conversely, a 46% decrease in mortality was observed during follow-up. One may find this result odd and counterintuitive. However, as described above, 41.8% of patients experiencing an infection benefited from a heart transplant, significantly more than in the no-infection group (26.4%, $P < .001$). Indeed, the French policy of heart transplantation attributes a high national priority for those patients having an LVAD-associated infection, prompting LVAD explantation and heart transplantation in such patients. Patients without infections consequently have a longer waiting time before transplantation under LVAD support and may end up dying from another cause. Lastly, despite this absence of influence on mortality, one has to keep in mind that LVAD-associated infection has a detrimental impact on patients' quality of life, because it requires more hospitalizations and care to overcome the infectious state.

Limitations

Our study has limitations. First, although data were prospectively collected in medical files, the study was retrospective. Hence, data collection and microbiological investigations were not standardized. However, all patients who receive LVAD had a systematic follow-up at the referral center every 3 to 6 months.

Second, only patients implanted in French centers were included, and our findings may not apply to other countries with different practices, different case mix, or different bacterial epidemiology. In addition, local protocols for wound care at the site of driveline exit differed among centers and were not collected in this study.

Third, because of the observational design, this study has many potential biases, especially regarding the comparability of patients implanted with HeartMate II and HeartWare. Although HeartMate II remained predictive of LVAD-specific infections in multivariable analysis, causality cannot be inferred, as we may have missed confounding factors. Lastly, our study focused on LVAD-specific infections (ie, percutaneous driveline, pocket, and/or pump/cannula infections) but collected no information on nonspecific LVAD-associated infections, as defined by the International Society for Heart and Lung Transplantation (ie, endocarditis, bloodstream infections, and mediastinitis). However, this contemporary study on LVAD-specific infections in patients with continuous-flow LVAD is the largest published thus far in this specific topic, having enrolled a large number of patients implanted with HeartMate II (n = 475) and HeartWare (n = 127) and is the first to document a lower risk of infections with third-generation LVAD.

Lastly, the antibiotic treatment used for LVAD-associated infections (molecule used and duration of therapy) was not collected in this study, and in consequence, we cannot give recommendations regarding the optimal drug therapy for a given infection/pathogen.

Conclusions

Left ventricular assist device still carries a high risk of infectious complications, even with contemporary continuous-flow devices. Most cases involve the percutaneous driveline, with a predominance of staphylococci, *Pseudomonas* species, and *Enterobacteriaceae*. Independent risk factors for LVAD-specific infections include HeartMate II implantation (as compared with HeartWare) and ICD-related procedures (ie, implantation, extraction, or replacement) post-LVAD.

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Disclosures

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References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics—2017 update: a report from the American Heart Association. Circulation 2017;135(10):e146-603.
2. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6(3):606-19.
3. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345(20):1435-43.
4. Holman WL, Naftel DC, Eckert CE, et al. Durability of left ventricular assist devices: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 2006 to 2011. J Thorac Cardiovasc Surg 2013;146(2):437-41. e1.
5. de By T, Mohacsi P, Gahl B, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report. Eur J Cardiothorac Surg 2018;53(2):309-16.
6. Bejko J, Toto F, Gregori D, et al. Left ventricle assist devices and driveline's infection incidence: a single-centre experience. J Artif Organs 2018;21(1):52-60.
7. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transpl 2015;34(12):1495-504.
8. Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transpl 2017;36(10):1080-6.
9. Xie A, Phan K, Yan TD. Durability of continuous-flow left ventricular assist devices: a systematic review. Ann Cardiothorac Surg 2014;3(6):547-56.

10. Simeon S, Flecher E, Revest M, et al. Left ventricular assist device–related infections: a multicentric study. Clin Microbiol Infect 2017;23(10):748-51.
11. Stulak JM, Davis ME, Haglund N, et al. Adverse events in contemporary continuous-flow left ventricular assist devices: a multi-institutional comparison shows significant differences. J Thorac Cardiovasc Surg 2016;151(1):177-89.
12. Leuck AM. Left ventricular assist device driveline infections: recent advances and future goals. J Thorac Dis 2015;7(12):2151-7.
13. Miller LW, Rogers JG. Evolution of left ventricular assist device therapy for advanced heart failure: a review. JAMA 2018;3(7):650-8.
14. Galand V, Flecher E, Auffret V, et al. Predictors and clinical impact of late ventricular arrhythmias in patients with continuous-flow left ventricular assist devices. JACC Clin Electrophysiol 2018;4(9):1166-75.
15. Hannan MM, Husain S, Mattner F, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transpl 2011;30(4):375-84.
16. Califano S, Pagani FD, Malani PN. Left ventricular assist device-associated infections. Infect Dis Clin North Am 2012;26(1):77-87.
17. O'Horo JC, Abu Saleh OM, Stulak JM, et al. Left ventricular assist device infections: a systematic review. ASAIO J 2018;64(3):287-94.
18. Koval CE, Thuita L, Moazami N, et al. Evolution and impact of drive-line infection in a large cohort of continuous-flow ventricular assist device recipients. J Heart Lung Transpl 2014;33(11):1164-72.
19. Kusne S, Staley L, Arabia F. Prevention and infection management in mechanical circulatory support device recipients. Clin Infect Dis 2017;64(2):222-8.
20. Gordon RJ, Weinberg AD, Pagani FD, et al. Prospective, multicenter study of ventricular assist device infections. Circulation 2013;127(6):691-702.
21. Chauhan D, Okoh AK, Fugar S, et al. Impact of left-ventricular assist device-related complications on posttransplant graft survival. Ann Thorac Surg 2017;104(6):1947-52.
22. Sharma V, Deo SV, Stulak JM, et al. Driveline infections in left ventricular assist devices: implications for destination therapy. Ann Thorac Surg 2012;94(5):1381-6.
23. Wert L, Hanke JS, Dogan G, et al. Reduction of driveline infections through doubled driveline tunneling of left ventricular assist devices-5-year follow-up. J Thorac Dis 2018;10:S1703-s10. Suppl 15.
24. Vidula H, Kutyifa V, Johnson BA, et al. Readmission patterns during long-term follow-up after left ventricular assist device implantation. Am J Cardiol 2018;122(6):1021-7.
25. Topkara VK, Kondareddy S, Malik F, et al. Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era. Ann Thorac Surg 2010;90(4):1270-7.
26. Riaz T, Nienaber JJ, Baddour LM, et al. Cardiovascular implantable electronic device infections in left ventricular assist device recipients. Pacing Clin Electrophysiol 2014;37(2):225-30.
27. Nienaber JJ, Kusne S, Riaz T, et al. Clinical manifestations and management of left ventricular assist device-associated infections. Clin Infect Dis 2013;57(10):1438-48.
28. Hanke JS, Rojas SV, Mahr C, et al. Five-year results of patients supported by HeartMate II: outcomes and adverse events. Eur J Cardiothorac Surg 2017;53(2):422-7.
29. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med 2017 Feb 2;376(5):451-60.
30. Clerkin KJ, Naka Y, Mancini DM, et al. The impact of obesity on patients bridged to transplantation with continuous-flow left ventricular assist Devices. JACC Heart Fail 2016;4(10):761-8.
31. Cagliostro B, Levin AP, Fried J, et al. Continuous-flow left ventricular assist devices and usefulness of a standardized strategy to reduce drive-line infections. J Heart Lung Transpl 2016;35(1):108-14.