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ORIGINAL ARTICLE

Artificial Heart (Clinical)

Left ventricular assist device-related infections: does the time of onset matter?

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Abstract

A frequent complication of left ventricular assist devices (LVAD) is the LVAD-associated infections (LVADIs). Contamination may occur during initial surgery/admission or at a later time. We studied the clinical manifestations and outcomes of LVADIs depending on the time of the onset. Patients implanted with LVADs at our institution between August 2009 and December 2014 were included. Patients were stratified into 2 groups based on whether the infection occurred early (< 180 days) or late (≥ 180 days) after LVAD implantation. Out of 37 overall LVADI episodes, 16 (43%) and 21 (57%) occurred early or late after device implantation, respectively. Median time to first LVADI was 88 ± 35 vs. 456 ± 187 days between groups. While superficial driveline-related infection was the most common LVADI type for both groups (56 vs. 71%, $p = 0.489$), driveline drainage was more prevalent in the late group (24 vs. 69%; $p = 0.009$). Early LVADIs involved more gram-positive flora, mostly Staphylococcus aureus (69 vs. 33%, $p = 0.049$), whereas late LVADIs involved more gram-negative pathogens, mostly *Pseudomonas aueroginosa* (25 vs. 57%; $p = 0.045$). High rates of treatment failure were consistent between groups (88 vs. 71%, $p = 0.384$). Compared with superficial LVADI, deeper infections were associated with an increase in mortality (13 vs 46%, $p = 0.046$). We concluded that early onset with likely in-hospital contamination involved more gram-positive flora, whereas late infection involved more gram-negative flora. Regardless of timing, success of antibacterial treatment was dismal, and infection depth correlated with poorer outcomes.

Keywords Ventricular assist device · LVAD · Infection

Introduction

Over 2 million people worldwide are estimated to have end-stage heart failure, and for many of them, a heart transplant would be life-saving. The prevalence of the disease is increasing, as is the number of patients who are eligible to receive a donor heart, but there is a definitive shortage of donor hearts available. For example, for every five patients to receive a heart transplant, it is estimated that one patient dies on the waiting list [1]. To bridge this gap, left ventricular-assist devices (LVAD) implantation evolved as a measure to prolong life prior to transplant. LVADs allow for the normalization of hemodynamics in the setting of a failing heart, which ultimately improves end-organ function and survival until heart transplantation can occur [2]. Today, they are still utilized in this role, in addition to being utilized as destination therapy or as a bridge to recovery.

In 2001, the REMATCH study demonstrated the efficacy of LVAD therapy. In this randomized, controlled trial, patients with end-stage heart failure implanted with the Heartmate-XVE® device exhibited a 48% reduction in the risk of death when managed with VAD therapy compared with those managed by optimal medical therapy [1, 3]. While these devices have earned a permanent position in today's treatment options for end-stage heart failure, they are certainly not without risk. One of the largest obstacles for successful LVAD device implantation is the frequency

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of infection. Despite the success of the REMATCH trial, the authors documented a 28% probability of infection within the first 3 months of device implantation with sepsis being the most common cause of death in this subset [3]. LVAD-associated infections (LVADIs) are serious complications that can prevent or delay transplantation for patients eligible to receive a donor heart, and significantly increase mortality for patients who receive an LVAD as destination therapy. Unfortunately, there is still a severe lack of data concerning the epidemiology, optimal prevention, and management of today's LVADIs, making ideal approaches to treatment difficult [2]. Furthermore, the majority of publications have been retrospective or single-center in nature and have not used consistent criteria to diagnose and characterize LVADIs. In 2011, the International Society of Heart and Lung Transplantation (ISHLT) did propose standardized consensus definitions to help stratify different types and clinical manifestations of LVADIs [4].

Recently, a retrospective analysis from a large, multicenter historical cohort of patients with continuous-flow LVADs revealed that driveline infections were the most common type of LVADI, and the authors noted a median time to the first infection of 4.4 months. *Staphylococci* and nosocomial gram-negative pathogens were the most frequent pathogens associated with infections, and endovascular infections presented earlier and with more severe clinical signs and symptoms. All-cause mortality was 43% at 2-year follow-up. Summarizing these results, the authors proposed a treatment algorithm for future management of LVADIs [5].

More recent studies have attempted to characterize potential risk factors involved in the development of LVADI, noting that younger patient age and driveline trauma correlate with higher incidences of LVAD-related infections [6]. Other studies have noted variations in time of LVADI onset, with median time to infection ranging anywhere from 1 to 6 months after device implantation [7]. However, no studies to date have compared the time of LVADI onset with respect to LVADI type and clinical outcomes. We saw several cases of infection developing within first few months after the implantation, and speculated that the contamination could occur during surgery or initial hospitalization. We further hypothesized that these early infections could have different presentation and prognosis that infections developing later. Our study looked to characterize the clinical manifestations, pharmacologic management, and outcomes of LVADIs at our institution, depending on the time of onset.

Methods and definitions

Patients ≥ 18 years of age implanted with LVADs between August 2009 and December 2014 with primary follow-up at our institution were screened for inclusion in this retrospective, single-center cohort study. Patients were included if an LVADI was documented and treated at our institution, and were stratified into two groups based on whether the initial infection occurred early (< 180 days) or late (≥ 180 days) after LVAD implantation. Besides, we stratified all LVADi into deep and superficial types.

LVADI was defined as all infections occurring in the presence of an LVAD that may or may not have been directly attributable to LVAD therapy but warranted special consideration because of the presence of an LVAD [4, 5]. Infections were identified by means of culture-positive documentation in the electronic medical records. Initial and subsequent LVADIs were classified based on the 2011 ISHLT consensus guidelines, and two main infection categories were delineated within our cohort, superficial and deep LVADIs [4]. For the purposes of our analysis, superficial LVADIs included localized driveline infections exclusively, while deep LVADIs encompassed all other infection types—including pocket, pump and/or cannula, and mediastinitis.

Additionally, infections were classified in terms of outcome—microbiological cure vs. treatment failure. Microbiological cure was defined as a resolution of any LVADI identified by consistently negative cultures after initiation of antimicrobial therapy. Treatment failure encompassed infection relapse, re-infection, or infection severity progression; for example, progression from driveline infection to a pump and/or cannula infection without microbiological cure of initial LVADI. An infection recurring at the same site, caused by the same organism within 1 year of treatment since the initial LVADI, and occurring after microbiological cure of initial LVADI was defined as infection relapse. A new infection with a microorganism distinct from the isolate recovered prior to therapy from initial LVADI was defined as re-infection [5]. Infections were also described in terms of pathogen type—gram-positive cocci (GPC), gram-negative bacilli (GNB), mixed (GPC and GNB), or fungal-associated infections—and were characterized based on results from blood, abscess, and/or wound cultures.

Time to initial LVADI was calculated starting from the date of device implantation to the date of first positive culture associated with clinical signs and symptoms of infection. At the time of device implant, each patient in the cohort received peri-operative antimicrobial prophylaxis therapy per institution protocol with rifampin, fluconazole, piperacillin/tazobactam, and vancomycin within 1–2 h prior to incision time, continued for 48 h post-implantation (levofloxacin was administered in place of piperacillin/tazobactam for penicillin-allergic patients). Mupirocin2% nasal ointment was applied to the nares 24 h prior to surgery and continued for approximately 1 week post-implantation. Long-term, suppressive antimicrobial therapy was continued in some patients at our institution after completion of primary intravenous antimicrobial treatment for the initial

LVADI to prevent relapse, re-infection, or infection severity progression in patients thought to have seeded the LVAD. Each LVADI included in this analysis was reviewed in detail by a team of LVAD nurse coordinators, clinical pharmacists, and cardiologists.

The primary endpoint was the incidence of LVADI type (superficial vs. deep) in relation to time of first infection onset (early vs. late). Secondary endpoints included the incidence of microbiological cure, relapse, or re-infection, the requirement for suppressive antimicrobial therapy, and clinically relevant outcomes (device explantation, heart transplant, and all-cause mortality) in relation to time of onset and depth of infection.

Statistical analysis

Baseline characteristics were summarized for the whole sample, the early onset group, and the late onset group as mean plus or minus standard deviation for quantitative variables and as number with percent for qualitative variables. Infection characteristics, treatment outcomes, and distribution of causative pathogens were compared between the early and late onset groups using a rank sum test for quantitative variables and Fisher's exact test for qualitative variables. Treatment outcomes were also compared between the superficial and deep infection groups using a rank sum test and Fisher's exact test. Data analysis and visualization were accomplished using Excel (Microsoft Corporation, Redmond, WA, USA), GraphPad QuickCalcs (GraphPad Software, La Jolla, CA, USA), and SAS (SAS Institute, Cary, NC, USA). A p value less than 0.05 was considered statistical significant.

Results

Out of 104 total patients followed who underwent LVAD implantation during the specified study period, we identified 37 overall initial LVADI episodes in 37 patients for inclusion. The overall infection rate was 35.6% within the study time period. Baseline characteristics including demographics, comorbidities, LVAD type, and objective clinical criteria are summarized in Table 1 for the LVADI group. The mean age at time of first LVADI was 51 ± 13 years, and 76% of patients were male. HeartMate II® was the most commonly used device (29 patients; 78%), and bridge to transplant was the more common indication for LVAD implantation (21 patients; 57%).

Table 1 Baseline characteristics of the study patients

Variable	Total (n = 37)	Early (n = 16)	Late (n = 21)
Age (years)	51 ± 13	51 ± 14	52 ± 13
Male gender	28 (76%)	14 (88%)	14 (67%)
Body mass index (kg/m^2)	32 ± 6	31 ± 5	33 ± 6
Comorbidities			
Coronary artery disease	11 (30%)	5 (31%)	6 (29%)
Diabetes mellitus	15 (41%)	6 (38%)	9 (43%)
Hypertension	18 (49%)	8 (50%)	10 (48%)
Smoker or previous smoker	18 (49%)	10 (63%)	8 (38%)
Device type			
HeartMate II®	28 (76%)	9 (56%)	19 (90%)
HeartWare®	8 (22%)	7 (44%)	1 (5%)
Implant goal			
Bridge to transplant	21 (57%)	12 (75%)	9 (43%)
Destination therapy	16 (43%)	4 (25%)	12 (57%)
SIRS criteria			
Systolic blood pressure (mmHg)	103 ± 21	100 ± 24	106 ± 19
Diastolic blood pressure (mmHg)	70 ± 16	69 ± 17	70 ± 16
Mean arterial pressure (mmHg)	80 ± 16	78 ± 18	82 ± 15
Heart rate (bpm)	87 ± 16	95 ± 16	81 ± 13
Temperature (°C)	37 ± 1	38 ± 1	37 ± 0.4
White blood cell count (k/uL)	10 ± 5	10 ± 6	10 ± 4
Blood glucose (average, mg/dL)	129 ± 43	146 ± 43	117 ± 40
Hemoglobin A1C (%)	6.1 ± 1.2	6.6 ± 1.5	5.6 ± 0.6
Albumin, mg/dL	6.8 ± 2.3	5.8 ± 1.9	6.1 ± 3.0
	99 ± 18.1	113 ± 22.5	121 ± 8.3
	6.0 ± 1.6	5.7 ± 3.2	5.4 ± 2.7
	1.8 ± 0.4	1.9 ± 1.1	1.7 ± 0.7

Out of 37 overall initial LVADI episodes, 16 (43%) and 21 (57%) of the initial LVADIs occurred early or late after device implantation, respectively. The median time to first LVADI was 84 [61–120] vs. 411 [296–556] days in the early vs. late LVADI groups. Superficial driveline-related infection was the most common LVADI type for both groups (56 and 71%, respectively, in the early and late onset groups, $p = 0.489$). Driveline drainage was part of clinical presentation in 24 and 69% of LVADI, respectively, $p = 0.009$. Deep infections occurred in 44 and 29% of LVADI, respectively, in the early and late onset groups, $p = 0.489$. LVAD-related bloodstream infections were significantly more common in early vs. late onset LVADI (44 vs. 10%, $p = 0.024$).

Early LVADIs involved more gram-positive flora, mostly Staphylococcus aureus (69 vs. 32%, $p = 0.049$), whereas late LVADIs involved more gram-negative pathogens, mostly Pseudomonas aueroginosa (25 vs. 68.4%; $p = 0.045$) (Table 2).

As shown in Table 3, high rates of treatment failure were noted in both groups: the early (88%) and the late onset (71%, $p = 0.426$) and the superficial vs. deep LVADI group (75% vs. 85%, $p = 0.384$). Among the types of treatment failure, infection relapse was the most common in each

Table 2 Bacterial flora in early and late LVAD-related infections

	N	Microorganism	Number (%)
Early infection	16	Gram positive	11 (68.8%)
		Methicillin resistant *Staphylococcus aureus*	7
		Methicillin susceptible *Staphylococcus aureus*	2
		Enterococcus faecalis	2
		Gram negative	4 (25.0%)
		Pseudomonas aeruginosa	3
		Escherichia coli	1
Late infection	19 (in two patients, the flora was mixed)	Gram positive	6 (31.6%)
		Methicillin resistant *Staphylococcus aureus*	3
		Methicillin *Staphylococcus aureus*	2
		Streptococcus pneumoniae	1
		Gram negative	13 (68.4%)
		Pseudomonas aeruginosa	10
		Klebsiella pneumoniae	1
		Proteus mirabilis	1
		Alcaligenes faecalis	1

Table 3 Treatment Outcomes (Early vs. Late; Superficial vs. Deep)

Outcomes	Early (n = 16)	Late (n = 21)	*p*-value	Superficial (n = 24)	Deep (n = 13)	*p*-value
Microbiological cure	2 (13%)	5 (24%)	0.426	6 (25%)	1 (8%)	0.384
Treatment failure	14 (88%)	15 (71%)	0.426	18 (75%)	11 (85%)	0.384
Relapse	9 (64%)	12 (80%)	0.427	15 (83%)	6 (55%)	0.379
Reinfection	0 (0%)	1 (7%)	1.000	0 (0%)	1 (9%)	0.198
Severity progression	5 (36%)	2 (13%)	0.215	3 (17%)	4 (36%)	0.375
All-cause mortality	3 (19%)	6 (29%)	0.705	3 (13%)	6 (46%)	0.046
Composite (all-cause mortality, explant, heart transplant)	12 (75%)	15 (71%)	0.705	17 (71%)	10 (77%)	1.000
Device explantation	1 (6%)	4 (19%)	0.376	4 (17%)	1 (8%)	0.634
Heart transplantation	8 (50%)	5 (24%)	0.090	10 (42%)	3 (23%)	0.292
Utilization of suppressive antimicrobial therapy	6 (38%)	7 (33%)	1.000	7 (29%)	6 (46%)	0.472
Initial parenteral antibiotics (vs. oral therapy)	11 (69%)	8 (38%)	0.099	9 (38%)	10 (77%)	0.038
Median [IQR] duration of antimicrobial therapy (days)	28 [14–39]	28 [20–35]	0.939	28 [14–35]	23 [16–42]	0.762
Median [IQR] time to first LVADI (days)	84 [61–120]	411 [296–556]	< 0.001	270 [101–501]	147 [90–377]	0.316

IQR interquartile range

subset of both groups (64 vs. 80%, $p=1.000$ and 83 vs. 55%, $p=0.198$, respectively). All-cause mortality was similar between early and late LVADIs (19 vs. 29%, $p=0.702$); however, deeper infections were associated with a significantly higher all-cause mortality than superficial ones (13 vs. 46%, $p=0.043$).

The cumulative incidence of LVAD explantation, heart transplant, and all-cause mortality was consistent among both groups (75 vs. 71%, $p=1.000$; 71% vs. 77%, $p=1.000$), as was the median duration of antimicrobial therapy in days [28 (14–39) vs. 28 (20–35), $p=0.939$; 28 (14–35] vs. 23 (16–42), $p=0.762$]. No distinct differences were noted regarding utilization of suppressive antimicrobial therapy between the early vs. late LVADI group (38 vs. 33%, $p=1.000$) or the superficial vs. deep LVADI group (29 vs. 46%, $p=0.472$). As opposed to oral antimicrobials, initial parenteral antimicrobial therapy was utilized more often for early LVADIs (69 vs. 38%, $p=0.099$); and significantly more often for deep LVADIs (38 vs. 77%, $p=0.038$). Patients who proceeded to heart transplantation had no episodes of infection relapse.

Discussion

Our retrospective, single-center study is the first one to compare LVADI time of onset with both LVADI type and respective clinical outcomes. Overall, we noted an infection incidence of 35.6% in patients who underwent LVAD implantation during the study period. These findings are consistent with recent data reporting other continuous-flow LVAD infection rates ranging from 32.8 to 47.4% [5, 8]. Superficial driveline-related infections were the most frequent type of LVADI in both early and late LVADI groups, as the driveline piercing the skin creates a continuous conduit for bacterial entry while the prosthetic driveline surface promotes biofilm formation [6, 9]. Within our cohort, driveline-related drainage or purulence was slightly more common with later LVADI presentation, likely due to the chronicity of device presence and prolonged opportunity for biofilm development and bacterial seeding.

Considering deeper infections, LVAD-related bloodstream infections were more likely to present earlier after LVAD implantation (within 180 days), and deep infections overall were shown to correlate with a statistically significant increase in mortality. Consistent with our findings, Nienaber and colleagues at the Mayo Clinic also noted earlier presentation of endovascular LVADIs (including pump and/or cannula infections, infective endocarditis, all BSIs, and cardiovascular implantable electronic device lead infections), at a median time of 1.6 months after implant and generally associated with more severe clinical signs and symptoms. These findings emphasize a high priority of appropriate diagnosis and initial treatment of LVADIs once they occur, and support the Mayo Clinic's proposed treatment algorithm hinging on prompt collection of blood cultures for all patients with suspected LVADI [5].

Regardless of timing or LVADI type, high rates of treatment failure were noted within our cohort, with infection relapse being the most common cause of treatment failure. While no formal guidelines exist of for the treatment of LVADIs once they occur, a general recommendation proposed by Neinaber et al. suggests 2–4 weeks of antimicrobial therapy with or without surgical debridement for driveline infections [5]. Our mean duration of antimicrobial therapy was similar among both groups and consisted of ~4 weeks in each subgroup. Typical empiric regimen included piperacillin/tazobactam 3.375 g intravenously every 6 h, Vancomycin 1500 mg intravenously × 1 dose followed by Vancomycin 1000 mg intravenously daily, Fluconazole 200 mg orally daily × 1 dose followed by Fluconazole 200 mg orally twice a day. Once the pathogen and sensitivity were determined, the regimen was adjusted accordingly. Interestingly, parenteral antimicrobial therapy was utilized significantly more often than oral therapy for deep LVADIs, but no distinct differences were noted in the utilization rate of suppressive antimicrobial therapy regardless of infection onset or depth.

While surgical debridement and source control are critical in the treatment of other device or hardware-related infections, LVAD pump exchange or device removal have generally been avoided and considered as a last-line option due to the increased morbidity and mortality associated with such procedures [10, 11]. Recently, however, device exchange or heart transplantation has been increasingly utilized to 'cure' LVADIs. While studies are limited documenting successful approaches for device exchange secondary to LVADIs, a 2015 study of 38 patients with active driveline-related LVADI received an orthotopic heart transplant and were found to have no difference in hospital length of stay, infections, or mortality after 30 months of follow-up [12]. Though we noted no differences in a composite endpoint of LVAD explantation, heart transplant, and all-cause mortality between either the early vs. late or superficial vs. deep group, due to the correlation noted between infection depth and early onset, in addition to infection depth and increased mortality, earlier pump exchange or listing for heart transplantation is increasingly being considered [13].

An interesting distinction between pathogen type and time of LVADI onset was noted in our cohort. While *Staphylococci* and *Pseudomonas* species are the more common overall culprits implicated in LVADIs within several studies, culprit pathogen as it relates to time to first LVADI has not been well described [5, 7, 13]. In our study, early LVADIs involved significantly more gram-positive flora, predominantly *Staphylococcus aureus*, likely due to in-hospital contamination and initial driveline site healing and/

or dressing changes. In contrast, late LVADIs favored more nosocomial gram-negative pathogen involvement, mostly *Pseudomonas aeruginosa*, likely reflecting the prolonged healthcare exposure and biofilm development that patients are subject to over time. Interestingly, it has been reported that taking shower can facilitate a Pseudomonas infection in lVAD recipients [14]. No fungal infections were noted within our cohort, and infection depth did not significantly affect the median time to first LVADI.

Conclusion

In summary, the clinical manifestations of initial LVADI may vary with respect to both the time of onset and type of LVADI. Earlier LVADI onset was associated with likely in-hospital contamination and involved more gram-positive flora, whereas late infection involved more gram-negative flora and was associated with increased driveline drainage/purulence. Regardless of timing, success of antimicrobial treatment was dismal, and infection depth correlated with poorer outcomes. Earlier surgical intervention with pump exchange or listing for heart transplantation may be considered as an earlier option in the treatment of LVADIs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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