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Early Adverse Events as Predictors of One-Year Mortality during Mechanical Circulatory Support

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Abstract

Background—Ventricular assist devices (VADs) provide effective treatment for end-stage heart failure, however most patients experience ≥ 1 major adverse event (AE) while on VAD support. Although early, non-fatal AEs may increase the risk of later mortality during VAD support, this relationship has not been established. Therefore, we sought to determine the impact of AEs occurring during the first 60 days of VAD support on one-year mortality.

Methods—A retrospective analysis was performed using prospectively collected data from a single-site database for patients aged ≥ 18 years receiving left- or biventricular support during 1996–2008, who survived > 60 days on VAD support. Fourteen major classes of AEs occurring during this 60-day period were examined. One-year survival rates of patients with and without each major AE were compared.

Results—There were 163 patients included; the mean age was 49.5 years, 80% were male, 87% were European American, 72% had left ventricular support, and 83% were bridge to transplant. The occurrence of renal failure, respiratory failure, bleeding events, and reoperations during the first 60 days after implantation significantly increased the risk of one-year mortality. Controlling for gender, age, VAD type, and intention to treat, renal failure was the only major AE significantly associated with later mortality (hazard ratio=2.96, $p=0.023$).

Conclusions—Specific AEs (renal, respiratory and bleeding events, and reoperations) significantly decrease longer-term survival, with renal failure conferring a 3-fold increased risk of one-year mortality. Peri-operative management should focus on strategies to mitigate risk for renal failure in order to maximize later outcomes.

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Keywords

mechanical circulatory support; heart failure; outcomes; mortality

Introduction

Ventricular assist devices (VADs) provide effective treatment for end-stage heart failure and can be utilized as bridges to transplantation¹⁻⁵, bridges to myocardial recovery⁶⁻⁷, or as destination therapy for patients who are not transplant candidates⁸⁻¹². The field of mechanical circulatory support is rapidly evolving with the development of more durable devices, leading to an increasing interest in utilizing VADs for extended support. In order to maximize patient outcomes, it is critical to have a comprehensive understanding of the variety of factors which adversely affect survival, particularly beyond the first several months after implantation. Although previous reports have documented the influence of patient characteristics prior to implantation on patient mortality¹³⁻¹⁶, the patient's clinical course while on mechanical support also has a substantial impact on survival¹⁷⁻²². In particular, the effect of early, non-fatal adverse events on longer-term survival has yet to be examined.

Currently, there is a high incidence of clinically significant adverse events (AEs) occurring during VAD support: approximately 80-90% of patients experience some type of clinically significant AE^{15,23}, with the most common being bleeding, infection, cardiac arrhythmias, and reoperations^{3-4,15,23}. The majority of these AEs occur within the first 1-2 months after implantation^{3,15,24-25}. Analyses of these early AEs are largely limited to the impact of a single AE^{18-20,26-29} on immediate patient mortality. However, the lasting consequences of these early, nonfatal AEs on longer-term survival have not been explored.

We hypothesized that clinically significant, but nonfatal, AEs that occur during the first 60 days after VAD implantation would have a negative impact on later-term survival. Therefore, utilizing standardized INTERMACS AE definitions^{23,30}, we sought to study patients on extended VAD support to determine the separate and combined effects of early AEs on one-year survival.

Methods

Subjects

Subjects included all patients aged ≥ 18 years who received left or biventricular mechanical support at the University of Pittsburgh Medical Center (UPMC) between January 1996 and December 2008. To capture a cohort with the potential for longer-term VAD implantation, we required that patients survive on VAD support for at least 60 days. Pulsatile devices utilized included the Novacor LVAS (WorldHeart Corp., Oakland, CA), HeartmateXVE LVAS (Thoratec Corp., Pleasanton, CA), and Thoratec paracorporeal or implantable VAD, used as either an LVAD or BiVAD (Thoratec Corp.). Continuous flow devices implanted were HeartMate II LVAD (Thoratec Corp.), VentrAssist LVAD (Ventracor, Australia), and Jarvik 2000 LVAD (Jarvik Heart Inc., New York, NY).

Study Design and Measures

This retrospective study of prospectively collected data was approved by the University of Pittsburgh Institutional Review Board. The data were extracted from the UPMC Cardiothoracic Transplantation Program's electronic database of prospectively collected data

on all mechanical support patients, supplemented by review of patients' UPMC medical records.

The primary study outcome was one-year actuarial survival while on ventricular support, assessed by time to patient death or to the end of patient follow-up (i.e., cardiac transplantation, successful weaning of the device, or continued VAD support at 12 months). The actuarial survival rate adjusts for patients' varied mortality risk exposure due to their different lengths of implantation, with censoring due to cardiac transplantation or weaning from the device.

Fourteen categories of clinically significant AEs occurring during the first 60 days post-implant were examined as possible predictors of mortality during the remaining year. These AEs, defined using INTERMACS criteria³⁰, have been detailed previously²³ and include clinically significant infections, bleeding events, respiratory events, neurological events, right ventricular(RV) failure, cardiovascular dysfunction, reoperations, cardiac tamponade, renal events, hepatic events, gastrointestinal events, hemolysis, thromboembolic events, and device malfunctions. Data on baseline patient demographics clinical characteristics, and causes of death were also collected.

Statistical Analysis

Descriptive information (including proportions, means, medians, and ranges) on patient demographics, VAD-related characteristics, and causes of death while on ventricular support were examined. The incidence of each type of major AE in the first 60 days of implant was determined. The association between the occurrence of AEs during the first 60 days of support and subsequent time to death was examined via survival analysis using the Kaplan-Meier procedure and the log rank test, with $\alpha=0.05$. Using all AEs that were at least marginally associated with survival ($p<.10$), a Cox Proportional Hazards model was then fit to the data to determine each AE's unique predictive effect within the context of other AEs. Thus, the main effects of each AE were first entered into the model. The interaction terms between pairs of AEs were added on a subsequent step in order to evaluate possible synergistic effects of combinations of AEs. Four baseline characteristics were controlled in the model: gender, age, intention to treat (bridge to transplant vs. other indications for implant), and type of VAD implanted (BiVAD, pulsatile LVAD, or continuous flow LVAD). The VAD type was controlled in the Cox model because survival may be altered by the implantation of an LVAD vs. a BiVAD^{12,14-15,31}. Moreover, by entering device flow pattern (pulsatile vs. continuous) in the model, we controlled for significant changes in patient management that occurred over recent years with the development of VAD technology. Before fitting this model, the predictors were examined and found to meet all analytical assumptions adequately. An $\alpha=0.05$ was used to determine statistical significance.

Results

Cohort Characteristics

A total of 163 patients (118 LVAD, 45 BiVAD) met inclusion criteria. The cohort was demographically similar to previously published cohorts of VAD patients in the U.S.^{3-4,12,15} Approximately 52% of patients presented with ischemic cardiomyopathy and 83% were implanted as a bridge to transplantation. Further details of the cohort's baseline characteristics are listed in Table 1.

One-Year Mortality while on VAD Support

The actuarial survival of the cohort through one year (i.e., adjusted for censoring in the observed duration of implantation due to transplantation or weaning from the device) was

60.2% (SE=5.9%). There were 35 deaths and their causes were classified into 7 broad categories, as shown in Table 2. The most frequent causes of death were CNS events (37% of deaths; mainly hemorrhagic and ischemic strokes), infectious events (31%; mainly sepsis and pneumonia) and multiorgan failure (11%).

Incidence of Clinically Significant Adverse Events

As shown in Table 3, the most frequently occurring AEs during the first 60 days after VAD implant were infection (experienced by 44.8% of patients), bleeding (44.2%), reoperations (33.1%), and cardiovascular dysfunction (38.0%). In comparison, some major AEs, including hemolysis, mechanical, gastrointestinal, hepatic, and thromboembolic events, occurred infrequently (<10% incidence rate) and therefore were excluded as predictors of survival. The AEs from Table 3 with incidence rates of at least 10% were examined in relation to one-year survival in both the univariable and multivariable analyses.

Univariable Analysis of Survival while on VAD Support

The cohort's one-year actuarial survival rates, stratified by the presence or absence of each of the nine AEs, are listed in Table 4. The presence of some AEs conferred a significantly increased risk of mortality. For example, one-year survival among patients who experienced early, acute renal failure was only 32%, compared to 65% ($p<0.001$) for those without renal failure. The survival curves for those with and without acute renal failure are shown in Figure 1 (panel a) demonstrating that the impact of early renal failure on later-term mortality begins immediately: the mortality curves begin to diverge at the start of the observation period and continue to separate over time. In addition to renal failure, respiratory events, bleeding events, and reoperations were associated with a significant decrease in cumulative survival through one year of VAD support; their respective survival curves are shown in Figure 1 (panels b-d).

We also examined one-year actuarial survival as a function of the total number of the nine different types of AEs each patient experienced (i.e., a simple count of how many unique types of AEs a patient had, ranging from 0-9). The patients were grouped into 4 categories depending on whether they experienced 0-1AE, 2-3 AEs, 4-5 AEs, or 6-8 AEs. (None of the patients experienced all 9 types of AEs in the first 60 days of implant.) Figure 2 demonstrates that a dose-response relationship emerged, with survival significantly decreasing as the number of types of AEs experienced by a patient increased.

Multivariable Analysis of Survival while on VAD Support

Two sets of Cox models were examined: one was fit for the entire cohort of BiVAD and LVAD patients, and a separate model one was fit for only LVAD patients in order to examine incident RV failure in this subgroup.

Beginning with the entire cohort, the main effects for all AEs that had p -values < 0.10 in the univariable analysis were entered into the model (i.e., renal, respiratory, bleeding, reoperation, and infection AEs), controlling for gender, age, intention to treat, and type of VAD implanted. The results, shown in Table 5, indicate that the occurrence of acute renal failure was the only significant predictor of one-year mortality, after controlling for baseline characteristics and the other AEs. Acute renal failure post-implant conferred a threefold increased risk of one-year mortality while on VAD support (hazard ratio=2.96, $p=.023$).

A second Cox model was fit for LVAD patients alone, in the same manner as the first model, in order to examine the effect of RV failure on mortality within the context of other AEs and baseline characteristics. The model (controlling for gender, age, intention to treat, VAD type) included renal failure, respiratory AEs, bleeding events, reoperation, infections,

and RV failure, with $\chi^2=19.97$ and $p=0.03$. Within this model, RV failure did not significantly increase one-year mortality ($p=0.177$).

In both models, interaction terms between pairs of AE variables were added in order to determine if unique combinations of AEs conferred greater risk for mortality. None of the interaction terms was found to be significant (all p -values >0.05).

Discussion

Few studies have investigated the impact of early, nonfatal AEs on longer-term VAD mortality²¹. Moreover, reports examining mortality generally focus on the effect of a limited group of AEs^{18-20,26-29,32-33}. The current study thus provides a unique investigation of the critical role of a full range of clinically significant, post-implant complications on longer-term mortality. We found that patients who experienced nonfatal episodes of renal failure, respiratory failure, bleeding events, and reoperations within the first 60 days of VAD support had significantly decreased one-year survival. Furthermore, our multivariable analysis demonstrated that early, acute renal failure while on VAD support was the strongest predictor of later-term mortality, conferring a threefold increased risk of death through the first year post-implantation.

The finding that some major AEs (i.e., neurological events and RV failure) did not predict longer-term mortality was unexpected. It has been well established that some of these AEs have a significant impact on peri-operative mortality. For example, it has been shown at many institutions, including our own, that the development of RV failure is associated with a significant increase in mortality during the first 30 days of implant^{18-19,34}. However, because we focused on patients who survived the first 60 days of implant, the present study excluded patients who experienced these early, mortal events. Thus, we were able to demonstrate that only a few of these early, nonfatal AEs were associated with greater risk of mortality beyond the peri-operative period.

Among these AEs, early respiratory failure requiring reintubation or tracheostomy significantly decreased the likelihood of later survival. Respiratory failure occurred in a quarter of our sample and, among these individuals, only 35% survived at one year (compared to 65% for those without respiratory failure). These respiratory AEs may be associated with episodes of decreased tissue oxygenation, increased RV afterload, risks of prolonged mechanical ventilation, and decreased mobility that contributes to deconditioning, all of which are likely to impact survival.

Bleeding remains one of the most common AEs following VAD implantation,^{3,15,23,35} and in a previous report we found that early bleeding events were particularly likely in BiVAD (compared to LVAD) patients.²³ The transfusions associated with significant bleeding events have been shown to increase infection risk, allosensitization, and acute lung injury³⁶⁻³⁷. The present study demonstrates that early, nonfatal bleeding events have a substantial impact on later-term mortality. Although patients with major bleeding events were successfully managed with transfusions and/or reoperations, their one-year survival rate of 48% was significantly poorer than the 71% survival rate in those without these events. Bleeding events often require multiple transfusions which may lead to acute lung injury and, in turn, can compromise RV function, increase the risk of end-organ ischemia, and require reoperations to ensure hemostasis.

Reoperations also confer an increased risk of mortality with a 48% one-year survival in those who required a major reoperation compared to a 68% survival rate for those who did not. We defined clinically significant reoperations as procedures for bleeding events and severe infections requiring debridement and/or flaps, and therefore their correlation with

decreased later survival may represent the impact of severe bleeding events and infections. Wound dehiscences indicate significant, chronic infections that are associated with a prolonged inflammatory response, deconditioning, and risk of sepsis, all which have longer term consequences on patient outcomes^{28,38}.

We also found that the development of acute renal failure early in VAD support was associated with a significantly decreased survival rate at one year. Chronic heart failure results in renal dysfunction via persistently elevated filling pressures, marginal cardiac output, and an adverse neurohormonal milieu³⁹⁻⁴⁰. Ventricular support restores end-organ perfusion, improves the neurohormonal milieu, and allows for more effective volume removal, all of which have salutary effects on renal function⁴¹⁻⁴⁴. However, a small proportion of patients (only 14% of our sample) will still develop renal failure while on VAD support^{3,12,23,35}. The development of renal failure after VAD implantation is particularly ominous: previous reports found a 6-month mortality of 71%-100% in such patients^{20,32-33}. The present study demonstrated that among patients who develop renal failure and survive the first sixty days, their prognosis for later-term survival is poor: only 50% of such patients are alive at 6 months and 30% at one year.

Since the set of AEs we examined are likely to be interrelated, we undertook further analysis to examine how the AEs act together to influence one-year mortality. First, we discovered a dose-response relationship between the total number of different types of VAD AEs experienced by the patient and mortality. Second, after controlling for gender, age, VAD type, intention to treat, we entered the subset of AEs that appeared to be the most important predictors of later mortality in order to determine the unique contribution of each AE. This model revealed that the strongest predictor of later-term mortality was the occurrence of renal failure within the first 60 days of VAD implant. Notably, patients who suffered from acute renal failure had a three-times increased risk of mortality during the study period.

The overriding impact of early renal events warrants further investigation into the mechanisms behind the development of acute renal failure post-implant in order to identify clinical targets to modify in daily practice. Other studies have suggested that the development of renal failure may be associated with a high risk presentation⁴⁵, where the insult to the renal system from prolonged periods of cardiogenic shock cannot be ameliorated by VAD support. We previously found that biventricular support, an indicator of patient acuity, was significantly associated with increased renal failure.²³ Others have suggested that the development of renal failure after VAD implantation is the result of pre-existing diffuse vasculopathy^{22,45}, which limits renal reserve and contributes to increased mortality.

Several limitations to our study must be acknowledged. Since this study was restricted to a single medical center, the size of our cohort was relatively small and thus limited our ability to perform more detailed analyses. For example, although a variety of VADs were implanted, we were only able to examine and control for general categories of device type (BiVAD, continuous flow LVAD, or pulsatile LVAD) in our analyses. In addition, we evaluated the effects of early, nonfatal adverse events largely assuming that each event occurred independently of the other or could be examined while statistically controlling for the impact of other events. In reality, the occurrences of adverse events are far more complex; multiple events may occur in a given patient and a single event may occur multiple times. Such an analysis is considerably complex and will need a more detailed examination as the focus of a future study. These limitations notwithstanding, our cohort reflects the typical VAD population at major medical centers with regard to demographics, incidence of VAD AEs, and causes of death, and we thus believe our findings can be extrapolated to other VAD populations.

As utilization of mechanical circulatory support continues to be employed as extended therapy, a complete understanding of the factors that predict longer-term survival is critical to maximizing patient outcomes. The analyses performed in the present study should be considered crucial in appreciating that even early adverse events may have lasting effects that can reduce later-term survival. Future work should also build on the findings of this study to delineate interactions and cascade of AEs and their subsequent impact on mortality.

In conclusion, we have demonstrated that the occurrence of nonfatal acute renal failure, respiratory failure, significant bleeding events, and reoperations within the first 60 days of VAD implant are associated with decreased one-year survival while on VAD support. Of these events, early renal failure is the strongest predictor of survival, tripling the risk of mortality. Our findings also emphasize the important impact of patients' early clinical course on longer-term outcomes, and thus continued monitoring of VAD AEs' effect is essential for future developments in ventricular support technology. The next logical step will be to closely examine how a full spectrum of pre-implant characteristics influences the risk of developing these critical adverse events and what post-operative management practices are needed to minimize their effects.

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Figure 1. Cumulative Survival Through 12 Month-Patient Survival Stratified by Absence or Presence of Clinically Significant Events

Figure 2. Cumulative Survival Through 12 months-Patient Survival Stratified by the Number of Types of Major Adverse Events

Table 1
Patient Demographics and Presenting Clinical Characteristics (n=163)

Characteristic	Descriptive Statistic
Gender(%)	
Male	79.8%
Female	20.2%
Age	
Mean $\pm$ SD	49.5 $\pm$ 13.1 years
min/max	18/71 years
Race (%)	
European American	86.5%
African American	11.0%
Other	2.5%
Outcome by 12 months (% , n)	
Transplanted	58.9% (n=96)
Died on Device	21.5% (n=35)
Still Implanted	12.9% (n=21)
Weaned	6.7% (n=11)
Device Type (%)	
LVAD	72.4%
<i>Pulsatile</i>	75%
<i>Continuous Flow</i>	25%
BiVAD	27.6%
Device(%)	
Thoratec BiVAD	27.6%
Thoratec LVAD	20.9%
Novacor	20.9%
Heartmate XVE	12.9%
Ventrassist	10.4%
Heartmate II	6.1%
Jarvik 2000 LVAD	1.2%
Diagnosis(%)	
Ischemic Cardiomyopathy	52.1%
Idiopathic Cardiomyopathy	38.7%
Inflammatory	7.4%
Congenital	1.2%
Hypertrophic Cardiomyopathy	0.6%
Intention To Treat (%)	
Bridge to Transplant	82.8%
Recovery Support	6.7%
Destination Therapy	6.1%
Postcardiotomy Failure	4.3%

Characteristic	Descriptive Statistic
Implant Era (%) *	
1996-2003	51.5%
2004-2008	48.5%

* Implant Era was divided at the beginning of 2004 due to introduction of continuous flow VADs during 2004.

Table 2
Causes of Mortality while on VAD support (total of 35 patients)

Cause of Death	Frequency (%)
CNS Event	13 (37.1%)
Cerebrovascular Accident	
Hemorrhagic	6 (17.1%)
Ischemic	6 (17.1%)
Intraoperative Air Embolism	1 (2.9%)
Infection	11 (31.4%)
Bacterial Sepsis	8(22.9%)
Bacterial Pneumonia	2 (5.7%)
Mediastinitis	1 (2.9%)
Multiorgan Failure	4 (11.4%)
Cardiovascular	3 (8.6%)
Arrhythmia	1 (2.9%)
Right Ventricular Failure	1 (2.9%)
Allergic Reaction	1 (2.9%)
Pulmonary: Respiratory Failure	2 (5.7%)
Malignancy: CNS	1 (2.9%)
Accidental Trauma	1 (2.9%)

CNS=central nervous system

Table 3
Incidence of Nonfatal Clinically Significant AEs during the First 60 Days of Implant
(n=163)

Clinically Significant Adverse Events	Percent (n) of Patients Experiencing ≥ 1 events	
Infection: Driveline, Blood Stream, Pulmonary, Mediastinum or Pocket	44.8%	(73)
Bleeding: Coagulopathy, Mediastinum, Pocket, Thorax, GI	44.2%	(72)
Cardiovascular Dysfunction: Ventricular (Vtach/Vfib), Atrial (SVT/Afib)	38.0%	(62)
Reoperations: Bleeding, Infection, Wound dehiscence, Wound debridement, Flaps	33.1%	(54)
Neurological Events: Hemorrhagic CVA, Ischemic CVA, TIA, Seizure, Coma	28.2%	(46)
Tamponade	26.4%	(43)
Respiratory: Tracheostomy, Reintubation	25.8%	(42)
Right Ventricular Failure (LVAD only, n=118)	19.6%	(32)
Acute Renal Failure	13.5%	(22)
Device Malfunction	8.6%	(14)
Thromboembolism	6.1%	(10)
Hepatic events	4.3%	(7)
Hemolysis	3.1%	(5)
Gastrointestinal events: Bowel perforation, Ischemic bowel	0%	(0)

VTach = ventricular tachycardia, Vfib= ventricular fibrillation, SVT= supraventricular tachycardia, Afib=atrial fibrillation, CVA= cerebrovascular accident, TIA= transient ischemic attack

Table 4
Actuarial Survival at 12 months (by Kaplan Meier) Stratified by the Presence or Absence of Early Nonfatal AEs

Adverse Event	Percentage Surviving on Device		Test of significance *
	≥1 AEs	No AE	
<i>Renal</i>	32.0%	65.1%	$\chi^2=15.464$ $p<.001$
<i>Respiratory</i>	35.3%	68.7%	$\chi^2=8.623$ $p=.003$
<i>Bleeding</i>	48.3%	70.9%	$\chi^2=4.945$ $p=.026$
<i>Reoperation</i>	47.9%	67.7%	$\chi^2=4.343$ $p=.037$
<i>RV Failure</i>	43.0%	66.7%	$\chi^2=3.714$ $p=.054$
<i>Infection</i>	53.9%	65.2%	$\chi^2=2.717$ $p=.099$
<i>Neurologic Event</i>	57.3%	60.6%	$\chi^2=1.026$ $p=.311$
<i>Tamponade</i>	58.0%	61.2%	$\chi^2=.001$ $p=.980$
<i>CV dysfunction</i>	57.7%	62.1%	$\chi^2=.000$ $p=.984$

* statistical test: log-rank analysis

Table 5
Multivariable Model of 12-Month Survival by Early Adverse Events, Controlling for Age, Sex, Intention to Treat, and Device Type. (model fit: $\chi^2 = 23.72$ $p=.008$)

Predictor Variable	Hazard Ratio	95% CI	p-value
Renal Event	2.96	[1.16, 7.57]	.023
Bleeding Event	1.52	[0.65, 3.55]	.337
Reoperation	1.19	[0.51, 2.81]	.689
Infection	1.17	[0.55, 2.51]	.681
Respiratory Event	1.35	[0.56, 3.25]	.504