Background—The use of ventricular assist devices (VADs) to bridge pediatric patients to heart transplantation has increased dramatically over the last 15 years. In this report, we present the largest US single-center report of pediatric VAD use to date. We present detailed descriptions of morbidity and mortality associated with VAD support, using standard Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria for pediatrics to facilitate the comparison of these results to other studies.

Methods and Results—We retrospectively identified 25 patients younger than 18 years with 27 episodes of mechanical circulatory support using VADs as bridge to heart transplantation from January 1998 to December 2007. Survival to transplant for the entire cohort was 74%. The most common major morbidities, as defined by INTERMACS criteria for a pediatric population, were respiratory failure, major localized infections, major bleeding events, hepatic dysfunction, and right heart failure. Major neurological events occurred in 48% of the study population. The median time to the first occurrence of an adverse event was less than 14 days for respiratory failure, right heart failure, major localized infection, and major bleeding. Patients who died before transplantation had significantly more adverse events per day of support than did those who were successfully transplanted. Episodes of major bleeding, tamponade, acute renal failure, respiratory failure, and right heart failure were all associated with increased risk of mortality.

Conclusions—INTERMACS criteria can be successfully used to analyze pediatric VAD outcomes. These data serve as a baseline for future studies of VAD support in children and indicate good survival rates but considerable morbidity. (Circ Heart Fail. 2010;3:682-688.) 

Key Words: pediatrics ■ congenital heart disease ■ mechanical circulatory support ■ INTERMACS
adult VAD survival rates and appear to represent a significant improvement over the 39% to 61% survival achieved with ECMO, although there may be confounding factors such as patient selection. The major morbidity reported during VAD support in children are bleeding events, infection, and neurological dysfunction.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is the major US registry for VAD clinical data. INTERMACS criteria to characterize implantation and describe morbidity have been developed to standardize outcomes reporting. Analyses using INTERMACS criteria have been performed on adult populations, but pediatric mortality and morbidity have yet to be described using the INTERMACS criteria. In the present report, we describe the results of 25 pediatric patients supported with 27 VAD between 1998 and 2007. To our knowledge, this is the largest US single-center report of pediatric VAD use for bridge to transplantation to date. We present detailed descriptions of morbidity and mortality associated with VAD support, using standard INTERMACS criteria for pediatric populations to facilitate the comparison of these results to future studies.

Methods

Patients

We retrospectively identified all patients younger than 18 years who received a VAD intended as a bridge to heart transplantation at Lucile Packard Children’s Hospital, Stanford University, between January 1, 1998, and December 31, 2007. This research protocol was approved by the Stanford University Institutional Review Board.

Data Collection

Demographic and clinical data were collected from medical records. For each day of VAD support, each patient’s medical record was reviewed and data were collected on adverse events, using standardized definitions per INTERMACS criteria for pediatric populations. Given the 10-year span of the study, we thought it would be valuable to compare early era and late era VAD recipients. The division was made at June 1, 2003, to create groups of equal size. Creatinine clearance (mL/min per 1.73 m²) was calculated from available laboratory data using the Schwartz method.

Statistical Analysis

All data are reported as mean±SD for normally distributed data and as median (range) for other continuous data. χ² was used for comparison of proportions in categorical data. One-way ANOVA or unpaired 2-tailed Student t test was used for comparison of continuous data. Kaplan–Meier curves were used to calculate actuarial and event-free survival. Competing risk analysis was performed to correct for noninformative censoring. Logistic regression and Cox proportional hazards models were used to generate unadjusted odds and hazard ratios, respectively, and to look for predictors of morbidity and mortality. The logistic regression analysis tracked time from institution of VAD support until the first occurrence of a specified adverse event to model event-free survival. The Cox proportional hazards analysis tracked patients from institution of VAD support until transplant or death and modeled the occurrences of a particular adverse event during that time period. Statistical significance was considered to be P<0.05. No attempts were made to correct for multiple comparisons due to the small sample size. Data were analyzed using Stata10 (StataCorp LP, College Station, Tex). Each VAD implantation was analyzed as an independent event because 2 patients received support from 2 different VADs at different times.

Results

Patient demographics and preimplantation and pretransplantation characteristics are summarized in Table 1. Twenty-five patients had 27 episodes of VAD support, for a total of 1206 days of therapy at Lucile Packard Children’s Hospital between January 1, 1998, and December 31, 2007, with approximately half the study group initiating support after June 1, 2003. The study population consists of 17 boys and 8 girls,
with a median age of 12 years (range, 3 months to 16.8 years),
including 3 patients younger than 1 year. The median weight
was 47 kg (range, 5.7 to 114 kg), including 7 patients
weighing <20 kg. Six patients were obese, with a body mass
index >25. The cause of heart failure was dilated cardiomy-
opathy in 18 patients, congenital heart disease in 4 patients,
hypertrophic cardiomyopathy in 2 patients, and restrictive
cardiomyopathy in 1 patient. Eight patients had previous
cardiithoracic surgery. Patients were critically ill at the time
of VAD implantation: 16 VADs were implanted for INTER-
MACS indication 1 (critical cardiogenic shock) and 10 VADs
were implanted for INTERMACS indication 2 (progressive
decline while on inotropic support). In 1 instance, the
implantation criterion could not be reliably determined from
the medical record.

As is shown in Table 1, patients were almost invariably
intubated and on inotropic support before implantation; 28%
had prior cardiac arrest requiring cardiopulmonary resuscita-
tion, and, of those, 71% were supported with ECMO (19% of
the total study population). All of the patients supported with
ECMO before VAD had a cardiac arrest. Support was
provided by Thoratec VAD (n=16), Berlin EXCOR (n=9),
another type of device (Biomedicus) (n=1), Novacor (n=1),
or unknown (n=1). One patient received the device at another
center before being transferred to Stanford, and his device
type is not precisely recorded in the available medical record.
One patient received a left-sided Thoratec VAD and a
right-sided Biomedicus device.

A left ventricular assist device (LVAD) alone was used in 20
patients, biventricular assist device (BiVAD) in 5 patients, and
right ventricular assist device (RVAD) alone in 2 patients. The
use of RVAD alone as a bridge to subsequent transplantation
was performed in 2 patients with acute postimplantation graft
failure. These patients were included as having right heart failure
for logistic regression analysis of the duration of adverse events;
however, because the heart failure predated the device, these
patients were not included in the multiple failure analysis with
Cox proportional hazards models.

Using the Kaplan–Meier method, survival was 83% at 30
days. Because this method censors patients at time of trans-
plant, it is more informative to show the results graphically
using the method of competing risk analysis (Figure 1). By
day 120 from institution of support, 70% of patients (19) had
received a transplant, 26% of patients (7) had died, and 4% of
patients (1) were on support awaiting transplant. This patient
still on VAD support on day 120 did receive a transplant on
day 237 of support. Patients were supported for a median of
26 days (range, 1 to 237). Duration of support was not
significantly associated with mortality. With respect to the
demographic, medical, and preimplantation characteristics
shown in Table 1, the sole criterion associated with mortality
was the ventricle receiving VAD support. Survival to trans-
plant with an LVAD alone was 85% compared with 65% for
patients receiving biventricular support and 0% for patients
receiving right ventricular support alone (P=0.024).

The incidence and frequency of INTERMACS adverse events
are summarized in Table 2. More than 50% of the patients had
each of the following adverse events: respiratory failure, major
localized infections, major bleeding events, hepatic dysfunction,
and right heart failure. Five adverse events were present on 20%
or more of support days: respiratory failure, right heart failure,
cerebrovascular accident (CVA), major localized infections, and
psychiatric episodes.
The average number of events per day of support is shown in Figure 2. Patients who died before transplantation had significantly more adverse events per day of support than those who survived to transplant (3.80 versus 1.76, \( P = 0.0025 \)). There was no significant difference in the percentage of support days on which an event occurred between the 2 groups (90% versus 81%, \( P = \text{NS} \)).

Table 3 summarizes the hazard ratio for mortality associated with the onset of each INTERMACS adverse event, allowing for multiple occurrences of each type of event in a single patient. Duration of an event is not incorporated into this analysis. Episodes of major bleeding, tamponade, acute renal failure, respiratory failure, and right heart failure were all associated with a hazard ratio >1, indicating that each event conferred an increased risk of mortality.

Using hazard ratios to investigate the onset of adverse events tends to underestimate the impact of events that last for extended periods of time; thus, we also performed risk analysis using odds ratios in which events are analyzed based on whether they are present or absent on any given day. This analysis, however, only allows for a single failure for each event. The results of this analysis are shown in Table 4. In comparison to the hazard ratios, this analysis identifies a greater number of factors associated with a statistically significant increase in the risk of mortality. These include, in addition to those identified through hazard models, ventricular arrhythmias, major localized infection, sepsis, ischemic or hemorrhagic CVA, and arterial non–central nervous system (CNS) thromboembolic events. The adverse events of hypertension and right heart failure were paradoxically associated with decreased risk of mortality. Specific causes of mortality are shown in Table 5. CNS events accounted for 43% of deaths.

**Discussion**

Recipient waiting times for heart transplantation can be quite prolonged, with important clinical sequelae. As a consequence,
VAD support as a bridge to transplantation has become increasingly common and, in adults, is now used in a substantial minority (>33%) of patients at the time of transplant.25

Our population had 74% survival to transplantation, comparable to survival reported in the literature for both adult17,18,21,22 and pediatric8,9,14,15 VAD support. CNS events, multiorgan failure, and cardiac failure were the leading causes of death in adult studies21 and were also causes of death in this pediatric population (Table 5).

Despite survival similar to reports in the literature, our population had a somewhat increased incidence of major adverse events compared with reported rates for adult and pediatric populations. The major morbidities reported during VAD support in children are major bleeding in 22% to 35% of patients, infection in 35% to 52%, and stroke or other neurological complications in 19% to 42% of patients.8,9,15,20 Of adults receiving VAD support, 35% had bleeding, 38% had at least 1 infection, and 18% had neurological dysfunction.18 In our population, 59% of patients had a major bleeding event, 63% had an infection with 44% having a septic episode, and 59% had neurological dysfunction with 48% having a CVA.

The reasons for discrepant adverse event rates between the various comparator studies and the present study are not entirely clear, but there are several potential factors that should be considered. It is likely that the clinical definitions of adverse events differ considerably from center to center, leading different centers to include different events in complication rates. The use of INTERMACS criteria in our study is intended to be a step toward eliminating this potential factor. Additionally, some of the complications we describe, for example, transient ischemic events (as distinct from CVAs) and major localized infections (in comparison to episodes of systemic sepsis), are not comprehensively described in other reports, limiting the basis for comparison.

Another factor that may influence results is that of patient selection. Our study spans a period of time during which VAD use in children has evolved rapidly, and, as a result, the selection criteria currently in use differ from those in place at the beginning of the data collection period. Even so, the patients

### Table 3. Unadjusted Hazard Ratios for Mortality for INTERMACS Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>95% Confidence Intervals</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction, acute</td>
<td>4.26</td>
<td>1.14–15.98</td>
<td>0.031</td>
</tr>
<tr>
<td>Tamponade</td>
<td>3.5</td>
<td>1.13–10.88</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>3.48</td>
<td>1.42–8.53</td>
<td>0.007</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>3.44</td>
<td>1.22–9.72</td>
<td>0.02</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.52</td>
<td>1.51–4.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial non-CNS thromboembolism</td>
<td>2.46</td>
<td>0.65–9.29</td>
<td>NS</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.61</td>
<td>0.85–3.05</td>
<td>NS</td>
</tr>
<tr>
<td>Major infection: localized, nondevice</td>
<td>1.35</td>
<td>0.69–2.63</td>
<td>NS</td>
</tr>
<tr>
<td>Supraventricular arrhythmia</td>
<td>1.22</td>
<td>0.30–5.01</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>1.03</td>
<td>0.33–3.20</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic or hemorrhagic CVA</td>
<td>0.92</td>
<td>0.29–2.89</td>
<td>NS</td>
</tr>
<tr>
<td>Percutaneous site and/or pocket infection</td>
<td>0.82</td>
<td>0.08–8.03</td>
<td>NS</td>
</tr>
<tr>
<td>Transient ischemic event</td>
<td>0.81</td>
<td>0.09–7.29</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.37</td>
<td>0.09–1.59</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>0.35</td>
<td>0.04–2.75</td>
<td>NS</td>
</tr>
</tbody>
</table>

Unadjusted hazard ratio for mortality associated with the onset of each INTERMACS adverse event, allowing for multiple occurrences of each event in a single patient.
in this study were mostly INTERMACS level I (62%). Although our data did not demonstrate a relationship between INTERMACS level and outcome of VAD support, this is probably too small a data set to define such a relationship. Other studies have shown that more severe illness severity at implantation correlates with adverse outcomes.21,22

Our results are for a particular era of VAD therapy but may not typify VAD use in the future as greater numbers of patients receive VAD support and as criteria for implantation evolve, perhaps including patients who are less critically ill. This raises the important and challenging question of when to initiate VAD support in children. To delay implantation unduly probably will increase the complication rate of VAD use and perhaps the mortality rate as well. On the other hand, premature use of VAD support raises the possibility of exposing excessive numbers of children to the complications of VAD therapy, some of whom might have otherwise received transplantation without requiring a VAD.

We believe that by reporting adverse events according to standardized INTERMACS criteria for pediatric populations, we will facilitate meaningful comparisons for future studies to help further elucidate the association between adverse events and survival to transplantation in pediatric patients receiving VAD support. Our results clearly indicate an association between important specific adverse events and survival as well as between the overall burden of adverse events and survival. Standardized criteria are particularly important in this setting because of the relatively small numbers of patients on VAD support at any one center.

One drawback to the INTERMACS criteria as currently written is that there is no differentiation between ischemic and hemorrhagic neurological events. We believe that a modified version of the criteria in which the difference is specified may improve the usefulness of future analysis in guiding clinical decision-making, especially with respect to appropriate levels of anticoagulation.

We chose to analyze the association of incidence and duration of INTERMACS adverse events with mortality because we believe that both analyses offer important insight into the impact of INTERMACS adverse events on patients’ clinical course and mortality. The hazard model allows for multiple failures, whereas the logistic regression takes into account duration of events. Some events occur rarely, but, when they do occur, exert an effect over a long period of time, whereas other events occur frequently and may predispose to more events of the same type. Additionally, idiosyncrasies in the INTERMACS definitions may lead to artifacts in the data such that events are coded for a longer or shorter duration or more or less frequently than is clinically relevant. Bearing this in mind, it is important to recognize that these analyses cannot prove a causal relationship between the INTERMACS adverse events and patient mortality.

Although death occurred in 7 patients, it was infrequent from the standpoint of survival analysis occurring on only 7 of 1206 days of support, so there are few conclusions about causes of death that can be drawn from this small sample.

Studies in adults have found that risk factors for mortality include older age, ascites, increased total bilirubin, cardiogenic shock as an indication for device implantation, and right heart failure treated with a BiVAD.17,21,26,27 Previously reported risk factors for mortality in pediatric VAD patients include younger age, congenital heart disease, earlier date of implantation, female sex, and preimplantation liver function.8,9,14 The use of an LVAD versus a BiVAD has not been found to influence survival in pediatric populations.8,9 None of these characteristics was significantly associated with mortality in our cohort; however, right heart failure treated with an RVAD or a BiVAD was significantly associated with mortality, due in part to the use of RVAD alone in 2 cases of acute posttransplantation graft failure with reinstitution of support. The numbers in this comparison are small and may be swayed by chance. A more definitive examination of the hazard of biventricular and right ventricular support in children will require a larger series. Of note, the INTERMACS data base is currently less complete for pediatric patients than it is for adults. As the INTERMACS data set expands to include a larger number of pediatric patients, a logical next step will be to perform analysis on this more contemporary population representing the experience of multiple centers.

This cohort also demonstrates that it is possible to successfully bridge complex patients with poor prognostic factors. Of the 3 patients with total bilirubin levels >4 mg/dL in the 48 hours before implantation, 1 was successfully bridged to transplant. Of the 6 patients with plasma creatinine levels >1.5 mg/dL in the 48 hours before implantation, 5 were successfully bridged to transplant, and of the 4 patients with creatinine clearance <50 mL/min per 1.73 m² in the 48 hours before implantation, 3 were successfully bridged to transplant. Although this does not represent the ideal strategy, it is reassuring to know that VAD implantation can be successfully conducted even in very challenging circumstances.

The present report does not attempt to answer the question of when to initiate VAD support. This remains a challenging clinical decision that depends not only on VAD outcomes but also on outcomes from the alternative of advanced medical therapy, as well as additional factors such as anticipated waiting times. Ideally, such an important issue would be addressed with a randomized trial, but such a trial does not appear feasible at the present time. In the absence of any randomized clinical trial data pertaining to this issue, reports such as these offer the only guidance available for this problem. The utility of these reports depends heavily on understanding precisely who received VAD support and what morbidity and mortality was associated with that support. For this reason, broad use of a standard set of definitions such as INTERMACS, for both implantation criteria and adverse events, is critical.

Sources of Funding

This study was supported by a Stanford Medical Student Scholars Fellowship.

Disclosures

Dr Rosenthal serves as a scientific advisor to Berlin Heart EXCOR.

References


**CLINICAL PERSPECTIVE**

Ventricular assist device (VAD) support as a bridge to transplantation has become increasingly common in adults and now so in pediatric populations. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria were created to standardize the reporting and discussion of morbidity in patients receiving mechanical circulatory support. This study is the first to our knowledge to examine the morbidity associated with pediatric VAD use and predictors of pretransplant mortality in this cohort using these INTERMACS-defined criteria. Our results indicate an association between important specific adverse events and survival as well as between the overall burden of adverse events and survival. Importantly, this cohort demonstrates that it is possible to successfully bridge complex patients with preexisting end-organ dysfunction, indicating that VAD support is a viable option for bridging critically ill patients who are perhaps too sick to undergo transplant at the time of presentation. Although this report does not attempt to answer the question of when to initiate VAD support, it does represent the first use of standardized criteria for reporting implantation criteria, adverse events and outcomes for VAD support in a pediatric population. As a randomized trial comparing VAD support with alternative medical therapies is unlikely at present, the use of standardized reporting criteria in this and future reports is critical for meaningful comparisons to support clinical decision-making.
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*Circ Heart Fail*. 2010;3:682-688; originally published online August 31, 2010;
doi: 10.1161/CIRCHEARTFAILURE.109.918672
*Circulation: Heart Failure* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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