Mechanical Circulatory Support for Advanced Heart Failure: Effect of Patient Selection on Outcome


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Mechanical Circulatory Support for Advanced Heart Failure: Effect of Patient Selection on Outcome

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**Background**—Use of wearable left ventricular assist systems (LVAS) in the treatment of advanced heart failure has steadily increased since 1993, when these devices became generally available in Europe. The aim of this study was to identify in an unselected cohort of LVAS recipients those aspects of patient selection that have an impact on postimplant survival.

**Methods and Results**—Data were obtained from the Novacor European Registry. Between 1993 and 1999, 464 patients were implanted with the Novacor LVAS. The majority had idiopathic (60%) or ischemic (27%) cardiomyopathy; the median age at implant was 49 (16 to 75) years. The median support time was 100 days (4.1 years maximum). Forty-nine percent of the recipients were discharged from the hospital on LVAS; they spent 75% of their time out of the hospital. For a subset of 366 recipients, for whom a complete set of data was available, multivariate analysis revealed that the following preimplant conditions were independent risk factors for survival after LVAS implantation: respiratory failure associated with septicemia (odds ratio 11.2), right heart failure (odds ratio 3.2), age >65 years (odds ratio 3.01), acute postcardiotomy (odds ratio 1.8), and acute infarction (odds ratio 1.7). For patients without any of these factors, the 1-year survival after LVAS implantation including the posttransplantation period was 60%; for the combined group with at least 1 risk factor, it was 24%.

**Conclusions**—Careful selection, specifically implantation before patients become moribund, and improvement of management may result in improved outcomes of LVAS treatment for advanced heart failure. *(Circulation. 2001;103:231-237.)*

**Key Words:** heart-assist device ■ heart failure ■ patients

Despite considerable advances in the diagnosis and medical treatment of heart failure, this condition remains the most common “malignant” disease in western society today.1,2 The Working Group on Heart Failure of the European Society of Cardiology has promoted a number of initiatives aimed at improving the treatment of heart failure.3 However, even the best combination of ACE inhibition, β-blockade, and diuretics is able to confer only up to a 16% survival benefit at 1 year, and this benefit disappears by year 5.4 How to treat the >50,000 patients per year worldwide who are aged <60 years and who develop advanced heart failure despite optimal medical therapy has not been resolved.5 The available donor supply limits cardiac transplantation to ∼3500 patients per year worldwide, and of these, <60% will survive >10 years, many with increasing morbidity. All the available evidence suggests that the donor supply is declining, implying an increasing gap between the supply and demand for heart replacement therapies.6 There is also evidence of a decreased survival benefit from transplantation compared with other forms of heart failure therapy.7 Xenografting, as a potential solution to this problem, has received widespread yet critical attention in recent years,8 whereas the more realistic solution of using mechanical circulatory support (MCS) systems has yet to be seriously considered.

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Drs Jansen and Wheelon are employees of World Heart Corporation. In addition, Dr Portner serves as Chairman Emeritus for Edwards LifeSciences, Novacor Division.

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Patients and Definitions
Between March 1993 and May 1999, 464 patients were implanted with the Novacor LVAS in 22 European centers, of which 11 centers have performed >10 implants each.

Because this model (N100 PC) was released in Europe as a commercial product, clinicians in participating centers were not bound by the constraints of an investigational protocol and predefined implantation criteria; thus, selection practices between centers varied greatly, with a large percentage of patients moribund at the time of implantation. One of the major purposes of the present study is to examine the consequences of a less rigorous patient selection.

Data were obtained from the Novacor European Registry. This Registry was instituted in 1997 at the instigation of a number of clinicians (European Advisory Board) who were active in the use of MCS in an endeavor to promote an evidence-based perspective in mechanically supported advanced heart failure patients. The format for data collection and definitions of complications were a result of an expert consensus process, and the system was refined over the subsequent years.

As yet, there are no internationally agreed definitions for complications in the field of mechanical circulatory assistance. Therefore, the European Advisory Board developed a set of definitions; the most important of which are listed here. Bleeding was defined as perioperative, related to the surgical procedure, and requiring reoperation or originating from anticoagulation imbalance occurring as digestive tract bleeding, late pump pocket bleeding, dental bleeding, or cerebral hemorrhage. Right heart failure was defined as cardiac index <2.0 L·min⁻¹·m⁻² with central venous pressure >18 mm Hg and with normovolemia, requiring intravenous dobutamine/dopamine >10 µg·kg⁻¹·min⁻¹ or support by a right ventricular assist device. Renal failure was defined as abnormal kidney function requiring replacement therapy (hemodialysis or filtration). Stroke was defined as a central nervous system deficit with sudden onset, persisting for >24 hours and confirmed by either conventional diagnostic methods (eg, CT scan) and/or at autopsy. Transient ischemic attacks (neurological events resolving within 24 hours) were excluded from the analysis because of the high degree of variability of diagnostic accuracy by clinical examination. Infection was defined as any positive culture for pathogenic organisms requiring antimicrobial therapy.

Data Analysis
Data were analyzed with SPSS (SPSS for Windows Release 9.0, SPSS Inc). Survival after LVAS implantation was defined as follows: currently supported, alive after transplantation, or alive after weaning from the LVAS. Continuous variables were expressed as medians with range. Binary variables were described by frequency distributions. In a subset of patients, for whom a more complete set of data was available (n=366), univariate analysis (Fisher exact test) and multivariate analysis (Cox proportional hazards regression analysis) were used to identify preimplant risk factors for mortality after LVAS implantation. Kaplan-Meier analysis was used to estimate survival probability over time. The incidence of clinical complications was analyzed in 4 time frames after LVAS implantation: (1) occurring in the first 30 days, (2) occurring from 1 to 3 months, (3) occurring from 3 to 6 months, and (4) occurring after 6 months.

Results
At the time of implantation, median age was 49 (16 to 75) years, with 5% of recipients aged >65 years. The majority of recipients were male (89%); body surface area was 1.92 (1.39 to 2.68) m². Diagnoses were dilated cardiomyopathy in 221 (60%) patients, ischemic heart disease in 100 (27%), acute myocardial infarction in 24 (7%), acute myocarditis in 19 (5%), and other causes in 2 (1%). Sixty-four (18%) patients had undergone prior thoracic surgical procedures. Preimplant

Figure 1. Diagram of wearable Novacor LVAS. Numbers indicate the following: 1, pump/drive unit; 2, valved conduits; 3, inflow conduit; 4, outflow conduit; 5, percutaneous lead; 6, filter; 7, compact controller; 8, primary power pack; and 9, reserve power pack. Implanted components are pump/drive unit, inflow conduit cannulating left ventricle, and outflow conduit anastomosed to ascending aorta. External components are compact controller coupled to pump/drive unit via percutaneous lead with filter and rechargeable primary and reserve power packs.

considered. There is a lack of prognostic data of patients supported by MCS systems. Therefore, the aim of the present study was to identify prognostic indicators of survival from a consecutive unselected cohort of 464 European recipients of the Novacor left ventricular assist system (LVAS).

Methods
LVAS Configuration
The Novacor LVAS was developed by Portner et al. in collaboration with Stanford University, and was used in the first successful LVAS bridge-to-transplant application in 1984. The pump drive unit is implanted below the diaphragm, anterior to the posterior rectus sheath, and connected in parallel to the natural circulation, taking blood from the left ventricle and returning it to the ascending aorta (Figure 1). Initially, the pump takes over the entire workload of the left ventricle, but usually some degree of native ventricular recovery and of ventricular ejection via the aortic valve occurs during exercise. Internal sensors allow the pump to track the output of the natural heart, providing automatic control, a degree of redundancy, and the possibility of removal should native ventricular recovery occur. Although early systems required a large console, a wearable version that is supported by a small electronic controller and by batteries worn on a belt was introduced in 1993.

In March 1998, a new inflow conduit was introduced, consisting of a knitted, gelatin-sealed, integrally supported, uncrimped polyester graft, replacing the previous inflow graft, which explant analysis had shown to be vulnerable to distortion and to have unfavorable flow characteristics. Comparative studies have demonstrated that this change has been associated with a significant reduction in embolic complications.
hemodynamic, renal, and hepatic data showed a pattern of cardiac decompensation despite maximal medical therapy: pulmonary capillary wedge pressure was 25 (2 to 45) mm Hg, and the cardiac index was 1.9 (0.6 to 3.7) L \cdot \text{min}^{-1} \cdot \text{m}^{-2}.

Serum creatinine levels were 1.3 (0.6 to 10.3) mg/dL, serum sodium was 135 (109 to 165) mmol/L, and total bilirubin was 1.7 (0.3 to 6.7) mg/dL. The intention to treat was as follows: bridge to transplant in the majority (321 recipients, 88%), followed by bridge to recovery (33 of 366 recipients, 9%), and definitive therapy (contraindication to transplant, 12 of 366 recipients, 3%).

Risk Factors
The clinical status of recipients at the time of implant (Table 1) illustrates their advanced condition. Univariate analysis of the preimplant clinical status showed that acute postcardiotomy status, respiratory failure, and right heart failure had a significant impact on 1-year survival. Subsequent multivariate analysis revealed that age at implant >65 years, preimplant acute myocardial infarction, preexisting right heart failure, acute postcardiotomy, and preimplant sepsis with concomitant respiratory failure were independent risk factors for survival after LVAS implantation (Table 2).

Survival Analysis
On the basis of this analysis, the recipient population was divided into 2 subgroups: 1 group included recipients without any of these risk factors (low-risk group, n=276, 75.4% of study population), and the other included those recipients with at least 1 of these risk factors (high-risk group, n=90, 24.6% of study population). The median LVAS support time was 100 (0 to 1477) days. Thirty-three recipients (9%) had been supported for at least 1 year; of these, 8 were supported >2 years, 2 were supported >3 years, and 1 was supported >4 years (Figure 2). In the high-risk group, 46 (51%) of 90 recipients were supported on LVAS for <30 days. The survival probability of each group is shown in Kaplan-Meier curves (Figure 3).

Table 3 shows the LVAS support duration related to outcomes. The median time to transplantation was 139 days in the low-risk group and 88 days in the high-risk group (P=0.133, not significant).

Morbidity
Of the recipients who received LVAS implants from 1996 to 1997, 23% were in the high-risk group. This percentage

### Table 1. Clinical Status at Time of LVAS Implantation

<table>
<thead>
<tr>
<th>Cases</th>
<th>Percentage</th>
<th>P (Fisher Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-aortic balloon pump</td>
<td>15.3%</td>
<td>0.058</td>
</tr>
<tr>
<td>Other ventricular assist</td>
<td>2.5%</td>
<td>0.187</td>
</tr>
<tr>
<td>Acute postcardiotomy*</td>
<td>3.8%</td>
<td>0.028</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>18.3%</td>
<td>0.043</td>
</tr>
<tr>
<td>Right heart failure</td>
<td>9.6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Dialysis</td>
<td>7.7%</td>
<td>0.114</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8.5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are from univariate analysis of survival after LVAS implantation.
*Failure to be weaned from cardiopulmonary bypass.

### Table 2. Predictors of Mortality After LVAS Implantation (Multivariate Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure and sepsicaemia*</td>
<td>11.18 (5.52–22.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preexisting right heart failure</td>
<td>3.16 (2.05–4.88)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at implant &gt;65 y</td>
<td>3.01 (1.76–5.15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Acute postcardiotomy</td>
<td>1.83 (0.91–3.68)</td>
<td>0.0879</td>
</tr>
<tr>
<td>Acute infarction</td>
<td>1.68 (0.96–2.96)</td>
<td>0.0698</td>
</tr>
</tbody>
</table>

Cox proportional hazards regression analysis was used (entry probability set at 0.10). Variables rejected from model include sex, intra-aortic balloon pump, dialysis, and prior thoracic surgery.

**Figure 2.** Number of patients and percentage of patients are shown for given duration of LVAS support in low-risk and high-risk groups.

**Figure 3.** Cumulative survival (see text for definitions) was significantly higher for low-risk group (log rank test, P<0.0001). Cumulative survival after 3 months and 1 and 2 years is summarized beneath graph.
increased to 31% in the more contemporary (1998 to 1999) group. However, despite the selection of sicker patients, there was a reduction in morbidity due to bleeding, right heart failure, bacteremia, and cerebral embolism (Figure 4). In the case of stroke, this reduction was associated with the introduction of a new inflow conduit. The temporal distribution of major complications experienced by this group of recipients is shown in Figure 5. Early bleeding complications were mainly perioperative and related to the surgical procedure and hepatic dysfunction. Bleeding complications after the first month were secondary to problems with coagulation management and were manifested as digestive tract bleeding, late pump pocket bleeding, dental bleeding, and cerebral hemorrhage. During the chronic phase of support, from 3 months on, infections of the driveline exit site, device pocket, and bacteremia occurred in 5% to 10% of patients. The predominant organisms cultured from driveline exit site and device pocket were *Staphylococcus* (46%) and *Enterococcus* (18%). In blood cultures, the predominant organisms were *Staphylococcus* (36%), *Enterococcus* (20%), and *Candida* (15%). Four patients with device valve endocarditis were successfully treated by replacement of the inflow and outflow valved conduits on postimplant day 6, 114, 490, and 1123, respectively. A fifth patient with valve endocarditis received a donor heart on day 464, 23 days after the diagnosis.

**Mortality**

The primary causes of death were sepsis (21%), multiple organ failure (18%), bleeding (15%), stroke (15%), and other (16%). No mechanical failure was encountered during the study period, which constituted 179 patient years. One pump was replaced electively after 1342 days because of impending deterioration of the pump drive. When the device was predicted to wear out within the following 2 months, 2 patients underwent cardiac transplantation at day 664 and 1297, respectively.

**Outpatients**

Of the recipients who were supported for at least 30 days, 49% were discharged from the hospital with their LVAS. This increased from 25% of the recipients in 1994 to 55% in 1999. The median time in the hospital until first discharge was 65 days, and the median time spent outside the hospital was 152 days, giving a cumulative out-of-hospital experience of 73.8 patient years. In total, 75% of the time on LVAS was spent outside the hospital environment, where the majority of recipients resumed their normal daily activities.

**Discussion**

Heart failure is now acknowledged to be the most common malignant disease in industrialized countries, with advanced heart failure having a worse prognosis than most forms of cancer. Transplantation provides the most effective therapy for this condition, but the shortage of donor organs results in <10% of potential recipients actually receiving a transplant. The Registry of the International Society of Heart and Lung Transplantation reports that 1-year posttransplant survival has remained ≈80% over the past 5 years, with a 5-year survival of ≈60% and thereafter a steady attrition rate of 4% per year.

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**TABLE 3. Outcome and Duration of LVAS Support**

<table>
<thead>
<tr>
<th></th>
<th>Low Risk (N=276)</th>
<th></th>
<th>High Risk (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Median Time on LVAS</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>d (Range)</td>
</tr>
<tr>
<td>Ongoing</td>
<td>37</td>
<td>13.4%</td>
<td>204 (24–1477)</td>
</tr>
<tr>
<td>Explanted</td>
<td>239</td>
<td>86.6%</td>
<td>84</td>
</tr>
<tr>
<td>Transplanted</td>
<td>134</td>
<td>56.1%</td>
<td>139 (6–1297)</td>
</tr>
<tr>
<td>Weaned</td>
<td>19</td>
<td>7.9%</td>
<td>73 (30–418)</td>
</tr>
<tr>
<td>Died*</td>
<td>86</td>
<td>36.0%</td>
<td>73 (0–591)</td>
</tr>
</tbody>
</table>

*Includes patients who died during implant procedure (19 of 366, 5.2%).

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Figure 4. Incidence of clinical complications in patients implanted between 1996 and 1997 and more recently, 1998 to 1999. Incidence of stroke has decreased significantly (*P*<0.05) in later cohort.
Furthermore, recent research suggests that the benefit from heart transplantation may be even lower than expected. In addition, long-term morbidity is not insignificant even at 1 year after transplant, with 70% of recipients encountering hypertension, 21% with renal dysfunction, 39% with hyperlipemia, 19% with diabetes, and 4% with malignancies. All of these complications show increasing prevalence with time.

The current generation of MCS devices has evolved from a program initiated by the US National Heart, Lung, and Blood Institute in the 1970s to develop long-term artificial heart devices. Two electrically powered pumps have emerged from this initiative; trials sponsored by the Food and Drug Administration for evaluating their safety and efficacy have recently been completed, and these pumps have received certification for commercial application in 1998. The pumps are the HeartMate 1205 VE (ThermoCardio Systems) and the Novacor N100 PC (World Heart Corp). Basic pump design has remained little changed over this development period, but power delivery and control have moved from large bedside consoles to wearable components, enabling patient autonomy in an outpatient setting. This has brought about substantial improvement in patient quality of life and a reduction in resource use.

Compared with medical treatment in a control group of patients, the Novacor was shown to confer a survival benefit of >80% two months after enrollment and >30% survival benefit 30 days after transplant in the same group of patients. A recent single-center report of a large cohort of transplant patients shows that the bridged transplant recipients demonstrated a survival benefit of >10%.

The Novacor N100PC LVAS received CE marking in Europe in 1993. This allowed unrestrictive use with regard to application and patient selection. Initial use was as a rescue therapy for transplant-eligible patients, and selection and management varied widely between centers. Therefore, the results from this early experience represent the learning phase of LVAS therapy. The present report illustrates that an acceptable 1-year survival and reduced morbidity is achievable with careful patient selection and optimal implant timing, consistent with findings from a previous single-center report. The preponderance of early complications, such as right heart failure, renal failure, stroke, and respiratory infections, suggests the strong influence of patient selection and reflects the preimplant morbidity. Extended utilization of intensive care is, besides its impact on resources, associated with an increased incidence of infection, with more problematic organisms and a spiral of negative sequelae. This has been independently studied by Gracin et al, who showed that MCS patients with a preimplant APACHE (Acute Physiology and Chronic Health Evaluation) score in the mid range (APACHE 11 to 20) had a larger survival benefit (40%) than either the very sick (APACHE >20, benefit 20%) or the minimally compromised (APACHE <10, 0% benefit). It is now well established that advanced heart failure is associated with a systemic inflammatory response that is interactive with both LVAS therapy and transplantation, compounding the already considerable challenges of recipient management.

Major morbidity has been declining as centers have gained wider experience with recipient management, despite the enrollment of sicker patients. The advantages of aprotinin and simpler surgical implant techniques have reduced surgical bleeding. More careful perioperative hemodynamic management and the use of inhaled nitric oxide have markedly reduced the incidence of right heart failure. Infection (in particular, driveline infection) rates are diminishing as a result of better prophylaxis and management of the exit site. However, infection has not proven to be a contraindication to thoracic transplantation. Replacement of valved-conduits for endocarditis has been straightforward because of the modular design of the system.

Design changes can have a major impact, as demonstrated by changing the inflow conduit to an uncrimped, integrally supported, and gelatin-coated graft, resulting in a 50% reduction in embolic complications. This experience illustrates that it has been possible to effect major improvements in outcomes by attention to detailed aspects of the therapy, and there is the potential for further improvement in the near future.

Mancini et al have recently demonstrated that LVAS patients can achieve a near-normal exercise response, equivalent to patients with mild heart failure, and Dew et al have shown that patients with a left ventricular assist device enjoy a quality of life that is comparable to that of transplant recipients.

Although the majority of Novacor applications have been as a bridge to transplant, a growing number of patients are now implanted with a view to recovery of native left ventricular function. A recent single-center publication has demonstrated that as many as 24% of supported patients may recover sufficient ventricular function to allow weaning from the LVAS. This has obvious implications for resource use and quality of life and could make a significant impact on the treatment of advanced heart failure, once the appropriate target population has been identified and optimal manage-
ment regimes have been established. The process of reverse remodeling of the unloaded left ventricle has to be studied in prospective multicenter trials.

The Novacor N100 LVAS has demonstrated a very high level of reliability and durability in the laboratory and in a wide variety of clinical settings, with no device-related failures in the study cohort. During routine surveillance of long-term support, 2 pumps were explanted because of the normal wearing out after >3 years, and 1 pump was explanted because of abnormal wear at nearly 2 years. In all cases, impending wearing out was diagnosed at least 2 months before anticipated potential failure.

Smaller, inexpensive, and less obtrusive blood pumps are undergoing development, and some are just entering clinical trials. However, although the potential benefits are encouraging, these designs still have to prove their durability, reliability, and physiological suitability for chronic applications. Transplantation is able to meet <10% of the need for cardiac replacement therapy, and outcomes have not improved over the past decade. Xenografting is also unlikely to provide a clinical solution within the next 10 years. The present study provides evidence for the efficacy of current LVAS therapy when applied to carefully selected and managed recipients. LVAS therapy provides the only practical alternative to heart transplantation today, and future device refinements promise to make a significant impact.

The data for this publication were extracted from the Novacor Registry, established in 1993. This registry was set up to provide data to facilitate clinical decision-making with respect to patient selection and management before and after device implantation, and it highlights aspects of the therapy that require attention. The potential value of an international registry of the entire spectrum of devices designed for prolonged (>30-day) MCS has been recognized by the Scientific Council on MCS of the International Society for Heart and Lung Transplantation. The council is currently working on establishing an international MCS registry and has adopted the data forms of the Novacor Registry as a template. This international registry would provide the additional benefit of enabling comparative assessments of efficacy between generic therapies and between individual devices, because definitions of outcomes and complications could be standardized. These data are critical to advancing our knowledge and our ability to provide an effective therapy for one of the most difficult and costly problems facing 21st century medicine, the treatment of the malignant syndrome of advanced heart failure.

Appendix

The following are contributing centers (in alphabetic country order): University Hospital Vienna, Vienna, Austria; University Hospital Saint Luc, Brussels, Belgium; Helsinki University Hospital, Helsinki, Finland; Hospital La Pitié Salpêtrière, Paris, France; Hospital Henri Mondor, Créteil, France; Hospital Laennec, Nantes, France; Hospital Brabois, Nancy, France; Hospital La Timone, Marseille, France; Hospital Trouseau, Chambry les Tours, France; Hospital Rangueil, Toulouse, France; Hospital Broussais, Paris, France; German Heart Center, Berlin, Germany; Heart Center Nordrhein Westfalen, Bad Oeynhausen, Germany; Westfalian Wilhelms University Hospital Münster, Münster, Germany; Hospital Großhadern, Munich, Germany; Hospital Ruprecht-Karls, Heidelberg, Germany; University Hospital, Freiburg, Germany; Hospital San Matteo, Pavia, Italy; Hospital Niguarda Ca’ Granda Milano, Milan, Italy; Hospital Padova, Padova, Italy; University Hospital Uppsala, Uppsala, Sweden; and Papworth Hospital, Cambridge, UK.

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