Extracorporeal Life Support to Left Ventricular Assist Device Bridge to Heart Transplant
A Strategy to Optimize Survival and Resource Utilization

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Background—The use of extracorporeal life support (extracorporeal membrane oxygenation [ECMO]) as a direct bridge to heart transplant in adult patients is associated with poor survival. Similarly, the use of an implantable left ventricular assist device (LVAD) to salvage patients with cardiac arrest, severe hemodynamic instability, and multiorgan failure results in poor outcome. The use of LVAD implant in patients who present with cardiogenic shock who have not been evaluated for transplantation or who have sustained a recent myocardial infarction also raises concerns. ECMO may provide reasonable short-term support to patients with severe hemodynamic instability, permit recovery of multiorgan injury, and allow time to complete a transplant evaluation before long-term circulatory support with an implantable LVAD is instituted. After acquisition of the HeartMate LVAD (Thermo Cardiosystems, Inc), we began using ECMO as a bridge to an implantable LVAD and, subsequently, to transplantation in selected high-risk patients.

Methods and Results—From October 1, 1996, through September 30, 1998, 32 adult patients who presented with refractory cardiogenic shock (cardiac index \(< 2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}\), with systolic blood pressure \(< 100 \text{ mm Hg}\) and pulmonary capillary wedge pressure \(\geq 24 \text{ mm Hg}\) and dependent on \(\geq 2\) inotropes with or without intra-aortic balloon pump) were evaluated and accepted as candidates for mechanical assistance as a bridge to transplant. Of the 32 patients, 14 (group I) had a cardiac arrest or severe hemodynamic instability (systolic blood pressure \(# 75 \text{ mm Hg}\) and evidence of multiorgan failure (defined as serum creatinine level \(> 3 \text{ mg/dL}\) or oliguria; international normalized ratio \(> 1.5\) or transaminases \(> 5\) times normal or total bilirubin \(> 3 \text{ mg/dL}\); and needing mechanical ventilation). Group I patients were placed on ECMO support; 7 underwent subsequent LVAD implant and 1 was bridged directly to transplant. Six patients in group I survived to transplant hospitalization discharge. The remaining 18 patients (group II) underwent LVAD implant without ECMO support; 12 survived to transplant hospitalization discharge and 2 remained alive with ongoing LVAD support and awaited transplant. One-year actuarial survival from the initiation of circulatory support was 43% in group I and 75% in group II. One-year actuarial survival from the time of LVAD implant in group I, conditional on surviving ECMO, was 71% (\(P = \text{NS}\) compared with group II).

Conclusions—In appropriately selected high-risk patients, the rate of LVAD survival after initial ECMO support was not significantly different from the survival rate after LVAD support alone. An initial period of resuscitation with ECMO is an effective strategy to salvage patients with extreme hemodynamic instability and multiorgan injury. Use of LVAD resources is improved by avoiding LVAD implant in a very-high-risk cohort of patients who do not survive ECMO.

Key Words: cardiopulmonary resuscitation • heart-assist device • transplantation • shock • survival • heart failure

Implantable left ventricular assist devices (LVADs; eg, HeartMate, Thermo Cardiosystems, Inc, and Novacor, Baxter, Inc) have greatly improved survival rates for patients in refractory cardiogenic shock who are awaiting heart transplantation.1–3 However, as with any intervention, success, to a large extent, is dependent on patient selection and care in appropriate clinical situations.4,5 In patients with cardiac arrest or severe hemodynamic instability associated with multiorgan failure, outcome after LVAD implantation may be poor.5 Implantation of an LVAD in a patient with recent (hours to days) extensive anteroapical myocardial infarction may increase technical complications, whereas implantation in a patient not evaluated for heart transplantation raises the concern that significant contraindications to heart transplantation might be identified after LVAD implant.

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For such patients, additional options for circulatory support can be provided to achieve immediate resuscitation. Extra- corporeal life support (extracorporeal membrane oxygenation [ECMO]) is a well-established technique for providing emergent circulatory support for patients with respiratory failure or cardiogenic shock.\(^6\)\(^7\) ECMO has several advantages: (1) the percutaneous approach is technically simple, rapid, and can be done at the bedside; (2) it provides both cardiac and pulmonary support for hypoxic patients; (3) it avoids a sternotomy incision; (4) it provides time to evaluate potential transplant candidates; (5) it applies to patients in cardiac arrest; (6) it avoids an apical ventriculotomy in patients with a recent large anteropapial myocardial infarction; and (7) it is relatively less costly than other forms of mechanical circulatory support. Despite these advantages, ECMO support has several disadvantages that limit its applicability as long-term circulatory support for a bridge to heart transplant. These limitations include the high incidence of complications with long-term support (ie, >7 days), limited duration of support, limited rehabilitation potential, significant risk of stroke, and need for anticoagulation.

The application of ECMO for immediate resuscitation followed by implantation of a LVAD may be a useful strategy for improvement of patient survival and use of LVAD resources because it offers the option of mechanical circulatory support to patients who are initially not acceptable candidates for an implantable LVAD. We reviewed our experience with 32 adult patients who presented at the University of Michigan Hospital System from October 1, 1996, to September 30, 1998, with cardiogenic shock that required mechanical circulatory support and who were treated first with ECMO or LVAD as a mechanical bridge to transplant.

**Methods**

A retrospective review of outcome was performed on 32 adult patients who presented at the University of Michigan Hospital System from October 1, 1996, to September 30, 1998, with refractory cardiogenic shock and who were treated with circulatory support by either ECMO to LVAD bridge to transplant or LVAD bridge to transplant. Initial screening criteria included the following: (1) refractory cardiogenic shock (cardiac index \( <2.0 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2} \) with systolic blood pressure \( <100 \text{ mm Hg} \) and pulmonary capillary wedge pressure \( >24 \text{ mm Hg} \) and dependent on \( \geq 2 \) inotropes with or without intra-aortic balloon pump), cardiac arrest, or high risk of eminent death (ie, recurrent life-threatening ventricular arrhythmia); (2) no existing absolute contraindications to heart transplantation; and (3) age \( \leq 65 \) years. Patients were divided into 2 groups on the basis of presenting degree of hemodynamic instability and organ injury. Group I consisted of patients who presented with cardiac arrest or severe hemodynamic instability (systolic blood pressure \( \geq 75 \text{ mm Hg} \) with evidence of multiple organ injury (defined as serum creatinine \( >3 \text{ mg/dL} \) or oliguria; international normalized ratio (INR) \( >1.5 \) or transaminases \( >5 \) times normal or total bilirubin \( >3 \text{ mg/dL} \); and who needed mechanical ventilation). Group II consisted of patients presenting with refractory cardiogenic shock with stable hemodynamics associated with evidence of organ injury in \( <2 \) organ systems. Group I patients were placed on circulatory support with ECMO with the intent to bridge to an LVAD and subsequently to heart transplant when clinically appropriate. Group II patients were placed on mechanical circulatory support with an LVAD (HeartMate; Thermo Cardiosystems, Inc), also with the intent to bridge to heart transplant.

Arterial inflow to institute ECMO support was obtained by right carotid artery cutdown in 7 patients and percutaneous femoral artery cannulation in 7 patients. One patient required arterial reinfusion to profundar artery of the distal extremity through a side port of the arterial inflow cannulae for limb ischemia. Venous drainage was obtained by right internal jugular cutdown in 6 patients and percutaneous femoral vein cannulation in 8 patients.

Atrial septostomy was performed in 5 of 14 (36%) patients placed on ECMO support. Early in the experience, atrial septostomy was performed in 3 patients after the development of pulmonary hemorrhage: 1 patient survived ECMO to LVAD implant. On the basis of this experience, atrial septostomy was performed after initiation of ECMO when the following existed: (1) echocardiographic evidence of left ventricular dilation and (2) pulmonary hypertension (mean pulmonary artery pressure \( >30 \text{ mm Hg} \) as assessed by Swan-Ganz monitoring. With the use of these guidelines, atrial septostomy was subsequently performed in 2 additional patients: 1 survived to LVAD implant, and the other was removed from ECMO support for preexisting, absolute contraindications to transplant unknown at the time of initiation of circulatory support. No further episodes of pulmonary hemorrhage occurred on ECMO with the use of our current indications for atrial septostomy.

Comparison of means was performed using the independent sample \( t \) test and Mann-Whitney test for nonparametric data. Actuarial survival was determined using the Kaplan-Meier method. Survival curves were compared by the log-rank test. Statistical significance was defined as \( P<0.05 \) without adjustment for multiple comparisons.

**Results**

No significant differences occurred in age, sex, or heart failure origin between groups (Table). Occurrence of cardiac arrest at the time of initiation of circulatory support was significantly \( (P<0.05) \) greater in group I. Cardiac arrest occurred in 1 patient in group II in the operating room just before initiation of cardiopulmonary bypass at the time of LVAD implant. Group I patients had a significantly increased incidence of mechanical ventilation before initiation of circulatory support, elevation of transaminases (lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase), and incidence of anuria or oliguria requiring subsequent hemodialysis or hemofiltration versus patients in group II. No significant differences occurred in the incidence of intra-aortic balloon pump support and levels of serum creatinine and blood urea nitrogen, INR, or total serum bilirubin between groups. At the time of initial presentation, Group I patients had significantly higher prognostic screening scale index\(^5\) values than did group II patients, which suggests worse LVAD outcomes if LVAD implantation was performed in all patients at the time of initial presentation.

Of the 14 group I patients, 6 died while on ECMO support, 7 survived to LVAD placement, and 1 with a postinfarct ventricular septal defect was directly bridged from ECMO to heart transplant and survived to discharge. Of the 6 deaths, 3 occurred in patients for whom ECMO support was withdrawn because of absolute contraindications to heart transplant that were not known to be present at the initiation of ECMO support. These included brain death, severe stroke, and active intravenous drug abuse. The 3 remaining deaths were attributed to complications that occurred while the patient was on ECMO support and included pulmonary hemorrhage (n=2) and technical difficulties at initiation of ECMO support (n=1). Of the 7 patients who survived to LVAD placement, 6 were placed on the HeartMate LVAD (5 vented-electric, 1
Implantable LVADs have greatly improved survival for patients in refractory cardiogenic shock awaiting heart transplantation.1–3 However, a group of patients remains who can benefit from mechanical circulatory support but who are very-high-risk LVAD candidates.4,5 In such cases, hemodynamic resuscitation and resolution of organ dysfunction by other means of mechanical circulatory support before LVAD implant, as well as performance of an adequate transplant evaluation, should improve LVAD and posttransplant outcomes.

ECMO is a well-established technology that provides circulatory support with the ability to resolve organ injury in patients who present with cardiac arrest or with severe hemodynamic instability associated with multiorgan failure.6,7 However, ECMO is not the only alternative to an implantable LVAD for providing emergency resuscitation to this group of patients. Other currently available options for emergency circulatory support include centrifugal pumps, the Abiomed BVS 5000 (Abiomed Inc), and the Thoratec ventricular assist device (Thoratec Laboratories Corp). However, ECMO offers some unique advantages in that it is readily available to rapidly resuscitate in-hospital patients with cardiac arrest. Fifty percent (Table) of the patients in the ECMO group in our report were in cardiac arrest at the time of initiation of ECMO support. Thus, instituting other forms of extracorporeal mechanical support in this clinical scenario was not as feasible. In addition, for our institution, ECMO is less costly than the other systems, does not require operating room resources, and avoids a sternotomy or ventriculotomy incision. Furthermore, no data currently suggest that ECMO is less efficacious for providing emergency circulatory support than the above-mentioned alternative systems.
The use of ECMO for cardiac failure in adult patients has limitations. One concern is that left ventricular decompression may be inadequate and thus result in pulmonary hypertension, edema, and hemorrhage. To address this concern, we routinely have obtained a transesophageal echocardiogram when pulmonary hypertension persists after initiation of ECMO support to assess filling of the left ventricular cavity. In cases in which the left ventricle is not adequately decompressed, we have performed an atrial septostomy (36% of cases). The second major concern of ECMO is the limited duration of support and the poor outcomes associated with long-term support in adults. The use of ECMO as a direct bridge to heart transplantation in adult patients has been avoided at our institution because the duration of support required while patients wait for a donor organ results in an unacceptably low success rate. The availability of the implantable LVAD to provide a readily available long-term bridge to transplant has alleviated this last concern.

The strategy of applying initial mechanical circulatory support with ECMO followed by bridging to an implantable LVAD appears to optimize patient survival while negating several of the principal limitations of each technology. Although ECMO provided for prompt resuscitation and resolution of organ injury and provided time to perform a transplant evaluation, the implantable LVAD provided a means for lower-risk, long-term circulatory support and rehabilitation. This strategy conserved LVAD resources and improved LVAD outcomes. Patients not surviving the initial period of ECMO support in all likelihood would not have survived LVAD support. Furthermore, in ≈20% of patients placed on ECMO support, clear absolute contraindications to heart transplant were identified. Thus, costly LVAD implantations in patients unlikely to survive or unlikely to be transplant candidates were avoided. Conversely, the availability of the implantable LVAD as an option for long-term, lower-risk circulatory support prompted more aggressive consideration and use of ECMO for patients who needed mechanical circulatory support. At our institution, ECMO is now routinely considered for patients experiencing in-hospital cardiac arrest who are potential heart transplant candidates.

The most important finding of this study was that LVAD survival after ECMO support in a group of critically ill patients was not different than in a group of patients undergoing only initial LVAD support. The major presumption in this study is that patients in group I were more ill and that LVAD implant was inappropriate at the time of evaluation or that its use would have been associated with poor outcome. Data are available that support this presumption. First, patients in group I had a higher incidence of multiorgan injury, manifested by increased incidences of intubation, renal insufficiency, and shock liver. Second, if the prognostic screening scale for LVAD outcomes developed by Oz and colleagues is applied to the cohort of patients at the time of initial presentation, group I patients had significantly higher values, which implies a predicted worse LVAD outcome than group II patients. Our favorable post-LVAD outcomes in these ECMO patients who underwent subsequent LVAD implantation suggest that ECMO provided sufficient resuscitation and recovery from organ injury to permit LVAD implantation at lower risk. However, despite equivalent survival rates, patients who underwent LVAD implant after ECMO support had significantly increased morbidity, manifested as increased right-side circulatory failure after LVAD implant and increased duration of LVAD support required for rehabilitation. We do not understand the basis for the increased

Figure 1. Actuarial survival (Kaplan-Meier; ±SE) for the entire cohort of patients (n=32) from the time of initiation of mechanical circulatory support.

Figure 2. Actuarial survival (Kaplan-Meier; ±SE) for groups I (n=14) and II (n=18) from the time of initiation of mechanical circulatory support (P<0.05, group I vs group II).

Figure 3. Conditional (surviving ECMO support) survival (Kaplan-Meier; ±SE) in group I patients after LVAD implant vs actuarial survival in group II (P=NS, group I vs group II).
incidence of right-side circulatory failure in the ECMO-LVAD group. This increased incidence could be attributed to a lung injury exacerbated by ECMO or may reflect the overall increased severity of illness and initial degree of hemodynamic insult to this group of patients.

An important consideration in the management of patients in group I is assessment of the degree of organ recovery and timing of the LVAD implant. Due to the finite period that ECMO support can be used without causing significant morbidity in the patient, it is unreasonable to expect complete resolution of all organ injury before the LVAD implant. If the prognostic screening score of Oz et al5 is again applied to group I patients just before the LVAD implant, only modest improvement is shown in the prognostic screening score (3.5 ± 1.6 compared with 4.1 ± 1.2 at the time of presentation), which suggests that incomplete recovery of organ function has occurred. This is particularly true in the case of renal failure, in which it is unlikely that significant renal dysfunction will recover during a short period of ECMO support. In such cases, we have presumed renal function will return once pulsatile flow is established with a LVAD and have not used renal function as a criteria to assess transplant candidacy or timing of LVAD implant. Recovery of pulmonary and liver function is a more important factor considered in the timing of LVAD implant. We have used an INR <1.5 and liver enzymes <5 times normal as important guidelines for the timing of LVAD implant. Total bilirubin is less important an indicator of timing of LVAD implant, given that we frequently observe sustained elevations in bilirubin levels that recover after LVAD implant. We have also observed that pulmonary compliance appears to be an important determinant of outcome: in ECMO patients with a sustained deterioration in pulmonary compliance (<25 cm²/cm H₂O), ECMO and LVAD outcome appears poor.

In summary, ECMO to LVAD bridge to heart transplant therapy provides an alternative means of circulatory support for patients who might not otherwise be candidates for an implantable LVAD or who represent a very high-risk for poor outcome. ECMO to LVAD bridge to heart transplant therapy improves utilization of LVAD resources by avoiding LVAD implantation in circumstances for which poor outcomes can be anticipated.

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References
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