Extracorporeal life support in preoperative and postoperative heart transplant management

Christian A. Bermudez[1], D. Michael McMullan[2]

[1]Division of Cardiovascular Surgery, University of Pennsylvania Health System, Philadelphia, PA, USA; [2]Division of Cardiac Surgery, Seattle Children's Hospital, Seattle, WA, USA

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Correspondence to: Christian A. Bermudez, MD. Division of Cardiovascular Surgery, Hospital of the University of Pennsylvania, 3400 Spruce Street, 6th Floor Silverstein, Philadelphia, PA 19104, USA. Email: christian.bermudez@uphs.upenn.edu.

Abstract: Increased experience with extracorporeal life support (ECLS) as a mode of cardiac support has expanded its use to diverse patient populations including patients requiring a bridge to heart transplantation and patients requiring posttransplant support for primary graft dysfunction (PGD). The use of ECLS is associated with acceptable outcomes in well-selected patients. While outcomes with the use of extracorporeal membrane oxygenation (ECMO) as a bridge to heart transplant have been variable, several series have confirmed the safe use of ECLS to stabilize patients prior to left ventricular assist device (LVAD) implantation. These patients are then considered later, when in stable condition, for heart transplant. When ECLS is used prior to heart transplant, mortality is greatest during the first 6 months posttransplant. Patients who are alive 6 months after transplant appear to have similar survival rates as patients who were not supported with ECLS prior to transplant. ECLS support is a reliable therapeutic option for severe PGD and early graft failure after heart transplantation. In patients who require support for severe PGD, venoarterial-ECMO appears to result in better clinical outcomes than LVAD support. ECLS use for PGD after heart transplant continues to be the first line of support. Further studies are necessary to understand the optimal role of ECLS in heart transplantation.

Keywords: Extracorporeal membrane oxygenation (ECMO); heart transplantation; primary graft dysfunction (PGD); heart-assist devices

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Introduction

Heart transplantation is currently considered the best treatment alternative for patients with advanced heart failure that is unresponsive to medical therapy (1). Due to donor shortages and the current allocation policies, time on the waitlist for a donor heart can be prolonged with an increasing number of patients requiring left ventricular assist devices (LVADs) or extracorporeal life support (ECLS) as a bridge to heart transplant. ECLS technology has been used for decades, and was stimulated by the development of membrane oxygenators. Although ECLS was initially primarily used to provide respiratory support, it quickly became apparent that ECLS is an excellent method of providing circulatory support for patients with life-threatening heart failure. More recently, improvements in oxygenator, pump, and cannula technology have rapidly expanded the use of ECLS (2).

During the past decade, ECLS has been used to provide primarily cardiac support in ~40% of patients in the Extracorporeal Life Support Organization (ELSO) international registry (2). Increased experience with ECLS as a mode of cardiac support has led to expanded use in

diverse patient populations including patients presenting with cardiogenic shock (CS) following an acute myocardial infarction, patients with CS from other etiologies, patients unable to be weaned from cardiopulmonary bypass (post-cardiotomy failure), patients who require ECLS as a bridge to heart transplantation, and patients who require posttransplant support for primary graft dysfunction (PGD). Additionally, pediatric patients with congenital or acquired heart defects who fail to separate from cardiopulmonary bypass are increasingly being supported by ECLS as a bridge to recovery, bridge to a definitive form of mechanical support, or bridge to transplantation (BTT). Out of necessity, ECLS has evolved into the primary form of mechanical support for very young children who have few other options.

ECLS prior to heart transplant

With over 4,500 patients undergoing heart transplantation each year, the proportion of transplant recipients who received some form of mechanical circulatory support prior to heart transplant increased from approximately 22% at the turn of the millennium to 50% in the most recent era (1). In general, continuous flow LVADs are frequently utilized as a bridge to heart transplant in patients with rapid clinical and hemodynamic deterioration, because this strategy allows patient stabilization and heart transplant under controlled circumstances with comparable short- and long-term outcomes to those seen in patients who do not require support (3). Despite the observed increase in the use of mechanical cardiac support over time, the proportion of patients supported with extracorporeal membrane oxygenation (ECMO) remains small, with only 1.2% of heart transplant recipients receiving this form of ECLS prior to transplantation (1-3).

ECLS has been reserved for use in the advanced stages of heart failure when a durable LVAD is not an option (for example, when an LVAD is not available or when there are anatomical contraindications for LVAD use) and is frequently used in patients in critical condition with hemodynamic collapse or profound biventricular dysfunction. Outcomes with this use of ECLS immediately before heart transplant have been modest with variable results (4-6). Chung and colleagues described 70 adult patients who received ECMO with the intent to bridge to heart transplant; 31 patients (44%) were successfully in bridged to transplant. The study found that age >50 years, pre-ECMO cardiopulmonary resuscitation, and sequential organ failure assessment (SOFA) score >10 at ECMO initiation were significant independent predictors of unsuccessful bridging (4). In a recent retrospective analysis from the French National Registry (CRISTAL), 80 patients on a "high-urgency list" who were supported on venoarterial (VA)-ECMO as a bridge to heart transplant were compared with 866 patients who were not supported prior to transplant. The 1-year overall survival rate was lower in candidates on ECMO (52.2%) as compared with patients who did not require ECMO support (75.5%) The 1-year posttransplant survival was 70% in the VA-ECMO group and 81% in the comparison group. The study's authors concluded that transplantation provides a survival benefit in listed patients on VA-ECMO even if posttransplant survival remains inferior to that of patients without VA-ECMO and that transplantation may be considered to be an acceptable primary therapy in selected patients on VA-ECMO (5).

As a result of these studies, we expect worse outcomes in patients supported on ECMO as a BTT. The use of ECLS and other short-term support devices per se has been described as a risk factor for mortality when used directly prior to transplant (7), and for this reason, ECLS has been mostly used as a double bridge or bridge-to-bridge (bridge to LVAD) to stabilize patients before LVAD implantation when considering heart transplant in a staged fashion only in patients who regain an acceptable clinical condition after support (8,9). The primary approach in the United States has been to favor the use of a durable ventricular assist device (VAD) as a bridge to heart transplant while reserving the use of short-term mechanical circulatory support, including ECMO, mostly as a double-bridge to heart transplant (8-10). There are still a few occasions when ECMO is preferentially used directly prior to heart transplant, and these are mostly cases where an LVAD is not an ideal option including in patients with left ventricular (LV) hypertrophy, severe biventricular dysfunction, congenital heart disease or refractory ventricular arrhythmias. In these patients, ECMO continues to be used selectively as a BTT.

Since the first report by Pagani and colleagues of the use of ECMO as a "bridge to bridge" (11), several different series have confirmed the safe use of ECMO as a mechanism to stabilize patients prior to a durable LVAD implant who are then considered later, when in stable condition, for heart transplant (8-10). Survival with this double-bridge strategy has varied according to the patients selected, ranging from 30–80% survival after LVAD placement. Tran

and colleagues at UCLA reported 45% survival in patients supported on ECMO prior to different VAD options (12). Shah and colleagues (9) observed 1-year survival of 57%, and more recently Marasco observed 1- to 2-year survival of 75% in patients supported on VA-ECMO for CS (8). This was similar to survival in patients in whom an LVAD was placed directly with no ECMO support, suggesting that the use of ECLS as a bridge to VAD stabilizes end-organ dysfunction and reduces perioperative mortality after VAD implantation as compared with that traditionally reported in these "crash and burn" patients. Although this strategy is an acceptable bailout in patients with advanced hemodynamic deterioration, patients who undergo VAD implantation after ECMO stabilization may be subjected to LVAD complications, and only 20–40% of patients supported on ECMO followed by LVAD implantation may receive a heart transplant after LVAD support with adequate outcomes. An argument can be made that this bridge-to-bridge strategy, which is frequently used in transplant centers in the United States, increases the complexity and cost of the treatment and leads to fewer patients getting to transplant, as compared with some series from European centers. However, a counterargument is that this strategy allows the transplant community to improve organ utilization leading to better posttransplant survival, seen with LVAD placement.

In the adult population, LVADs have changed the landscape of mechanical support to bridge patients to heart transplant. In contrast, children with end-stage heart failure represent the largest group of patients who receive pretransplant ECLS. The lack of a pediatric VAD and the frequent anatomical variations in patients with congenital heart abnormalities limit the consideration of LVAD support in pediatric patients, and 16% of pediatric, heart-transplant recipients receive ECLS with or without additional mechanical support while awaiting transplantation (13). There is strong evidence that this level of invasive hemodynamic support is associated with increased risk of transplant-waiting-list mortality in children. Children who are supported with ECLS are twice as likely to die while waiting for a heart transplant as children who do not require ECLS and remain free from mechanical ventilation prior to heart transplant (14). The use of ECLS in pediatric patients is associated with 29% mortality after 1 month of waiting for a heart transplant and only a 39% overall likelihood of transplantation.

Increased waiting-list mortality is most apparent in young children who have fewer mechanical cardiac support options. The use of non-ECLS mechanical cardiac support (such as a VAD) in pediatric patients is associated with waiting-list survival rates similar to those observed in patients classified as United Network for Organ Sharing (UNOS) status 1 who do not require mechanical cardiac support (15). In a study of 431 pediatric patients (<19 years of age), posttransplant survival was better in patients who did not require mechanical cardiac support or who were bridged with VADs as compared with patients who were bridged to transplantation with ECLS (16). However, waiting-list survival is lower for younger patients on mechanical cardiac support. The survival rate for children <10 years of age who receive mechanical cardiac support is similar to that observed in children who are supported by ECLS while awaiting transplantation (14,15). Waiting-list survival appears to be somewhat better for children supported with newer extracorporeal, pulsatile, VADs, but use of these devices is associated with stroke in approximately 1/3 of patients (17).

Posttransplant mortality is greatest during the first 6 months after transplant, and patients who are alive 6 months after transplant appear to have similar survival rates as patients who were not supported with ECLS (13,16). Adults who are bridged with ECLS exhibit similar posttransplant survival curves, with an increased risk of early posttransplant mortality, but long-term survival similar to non-ECLS patients if they survive the initial posttransplant period (1). This suggests that underlying severity of illness plays an important role in determining survival. A prospective randomized study that compares ECLS with non-ECLS mechanical cardiac support prior to heart transplant has not been performed.

Except in very specific patient populations, such as neonates with univentricular forms of congenital heart disease, VADs appear to be the preferred form of pretransplant mechanical cardiac support. However, acute changes in clinical status may create uncertainty about a patient's candidacy for transplantation. For example, uncertainty about the neurologic status of a patient with end-stage heart failure who experiences the return of spontaneous circulation after a prolonged period of cardiac arrest may cause some to question the utility of initiating mechanical cardiac support with a durable VAD. In these situations, rapidly deployable, non-durable support with ECLS may provide life-saving hemodynamic stability. In many cases, the likelihood of myocardial recovery is unknown when ECLS is initiated. During this period of clinical uncertainty, ECLS is useful as a "bridge to decision"

about transplant candidacy, while neurologic function and end-organ recovery are assessed. Consideration should be given to transitioning potential transplantation candidates to VAD support (bridge-to-bridge) if myocardial recovery does not occur within 7–14 days. A recent retrospective review of 58 consecutive patients who were implanted with a continuous-flow, axial LVAD found no difference in survival between patients who were bridged to durable mechanical circulatory support with ECLS and those who underwent durable device implantation without ECLS bridging (8). The authors observed significant improvements in hepatic and renal function and concluded that ECLS stabilization improved end-organ function prior to durable device implantation and reduced perioperative mortality during durable device implantation.

In developing a management algorithm for providing mechanical support for patients with life-threatening heart failure, several factors must be considered including unique patient characteristics, such as age, underlying structural cardiac abnormalities, acuity of decompensation (if any), certainty of transplantation candidacy, and the likelihood of myocardial recovery. ECLS may be the best method of providing mechanical support for young patients with palliated or non-palliated univentricular heart failure. In other populations, ECLS appears to be an excellent method of providing rapid mechanical support in patients who experience refractory, life-threatening myocardial failure. When end-organ functional status has been determined in these patients, most patients should be transitioned to a more durable form of mechanical circulatory support if myocardial recovery is not eminent. ECLS is an excellent method for supporting patients with combined respiratory and myocardial failure, but consideration should be given to transitioning to more durable support options once ECLS is no longer needed to support respiratory function.

Prospective studies that compare various support modalities in different patient populations are required before data-based guidelines can be developed. Clinical data from all ECLS patients should be entered into large multisite registries, such as the ELSO international registry, to facilitate analysis and a better understanding of risk factors for mortality in patients with end-stage heart failure.

ECLS after heart transplant

PGD is a life-threatening complication after heart transplantation. Its incidence varies between 3–30%, depending on the series, and PGD accounts for 40–50% of early mortality seen after heart transplant according to studies using the International Society of Heart and Lung Transplantation (ISHLT) registry (1). Donor age, organ ischemic time, mechanical circulatory support [including right ventricular assist devices (RVADs)] prior to transplant, and congenital etiology in the recipient seem to be associated with a higher rate of PGD. Recently, a consensus statement, which attempted to better define PGD in heart transplantation, classified severe PGD as a need for mechanical circulatory support (other than an intra-aortic balloon pump) to maintain adequate end-organ perfusion following the procedure (18). Mechanical circulatory support can be provided by VA-ECMO or implantation of a temporary VAD. Although ECMO has been favored historically due to ease of implantation and the ability to provide oxygenation following a prolonged cardiopulmonary bypass, ECMO use is associated with increased risk of bleeding and insufficient LV unloading with a risk of intracardiac thrombosis in patients with minimal cardiac function (19,20). Other alternatives, including temporary LVAD support, have been considered more recently with the ability to provide better unloading, using direct ventricular cannulation and providing longer support to allow cardiac recovery. The device of choice and timing of insertion varies among institutions, and the use of mechanical circulatory support tends to be more liberal and favors early support in high-volume centers with a potentially positive effect on allograft recovery. In a recent analysis of 54 patients supported on ECMO for PGD in a large French center, 36 patients (67%) were weaned from the assisting device, and 27 of the patients supported with ECMO (50%) were discharged from the hospital (21). Overall conditional survival was 73% at 1 year and 66% at 5 years. The authors concluded that ECMO support is a reliable therapeutic option for severe, early graft failure after cardiac transplantation. Furthermore, patients treated with ECMO had the same 1-year conditional survival as patients who did not suffer PGD. In this study, the authors found no difference in weaning when comparing peripheral ECMO and central ECMO (50%), but higher rate of vascular complications (18%) in patients supported on peripheral ECMO.

More recently, Takeda and colleagues from Columbia University performed an analysis of patients requiring mechanical support for PGD following heart transplant (22). Of the 597 patients who received a heart transplant during the study period, severe PGD developed in 44 (7.4%). Within 24 hours of transplant, 17 of these patients received

support via a continuous-flow external VAD, and 27 received VA-ECMO support. The patients who received a VAD were more likely to have a longer support time, major bleeding requiring chest re-exploration, and renal failure requiring renal replacement therapy after surgery. In-hospital mortality was 41% for VAD patients and 19% for VA-ECMO patients. Ten patients (59%) were weaned from VAD support, and 24 patients (89%) were weaned from VA-ECMO support after adequate graft function recovery. The 3-year posttransplant survival was 41% in the VAD group and 66% in the VA-ECMO group, leading to the conclusion that for severe PGD, support with VA-ECMO appears to result in better clinical outcomes than VAD support. ECMO in patients with PGD or allograft failure due to other causes seems to be associated with better outcomes than ECMO support for other causes of CS. Tran and colleagues, from UCLA, demonstrated that patients requiring ECMO for heart transplant graft failure had lower mortality (51.6%) as compared with patients who required ECMO support for all other etiologies (69.1%).

Although ECMO can provide adequate support, it has limitations including limited LV unloading, limited time of support, and risks of thromboembolic and vascular complications. ECMO may be insufficient if an absence of recovery is noted, and other more aggressive strategies may be required, such as biventricular support including a durable VAD or a total artificial heart. There is a lack of evidence to support the use of these more radical alternatives, but the selection of a device should be made according to the patient's clinical condition and the center's experience.

Summary

Advances in ECLS have increased consideration of its use in patients with heart failure as a bridge to heart transplant and as postoperative support in heart transplant recipients with PGD to allow organ recovery. Today, the use of ECLS under these circumstances is associated with acceptable outcomes in well-selected patients. Although an LVAD usually provides a reliable platform and a more consistent outcome in patients supported while waiting for a heart transplant, ECLS is increasingly used in patients in whom LVADs are not reliable, including patients with restrictive cardiomyopathy, refractory arrhythmia, or in patients who are likely to receive a heart transplant within a short time after listing. ECLS use for PGD after heart transplant continues to be the first line of support with some recent evidence of improved outcomes as compared with short-term VAD use. Further studies are necessary to understand the optimal role of ECLS in heart transplantation.

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Footnote

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