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# Extracorporeal Membrane Oxygenation Support as Treatment for Early Graft Failure After Heart Transplantation

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/64040>

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## Abstract

Early graft failure (EGF) is a major risk factor for death after heart transplantation (Htx) accounting for >40% of deaths within 30 days postoperatively. According to the last International Society for Heart and Lung Transplantation (ISHLT) consensus statement, the graft dysfunction (GD) is to be classified into primary (PGD), in case of an unknown triggering factor or secondary (SGD) where there is a discernible cause such as acute rejection, pulmonary hypertension, or known surgical complications. The diagnosis of GD is to be made within 24 h after completion of Htx surgery and a severity scale for GD should include mild, moderate, or severe grades based on specified criteria. Mechanical circulatory support (MCS) for GD should be considered when medical management is not sufficient to support the newly transplanted graft. Currently, extracorporeal membrane oxygenation (ECMO) is widely accepted as treatment of severe EGF, given its easy and quick setup, the system versatility, the optimal end-organ perfusion provided, and the possibility of both biventricular and lung assistance by usage of a low-cost single pump.

**Keywords:** heart transplantation, early graft failure, cardiogenic shock, mechanical circulatory support, extracorporeal membrane oxygenation

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## 1. Introduction

A recent examination of early mortality after heart transplantation (Htx), documented in the International Society for Heart and Lung Transplantation (ISHLT) Registry, reveals that >40% of deaths within 30 days post-operatively are due to early graft failure (EGF) [1, 2]. Results get even worse in the pediatric transplant population where an early mortality of 88% after diagnosis has been reported [3]. To better define the classification, diagnosis and management of this condition, a Consensus Conference was organized on April 23, 2013 during the 33rd Annual ISHLT meeting. There were 71 specialists on this field including cardiologists, immunologists, pathologists, and surgeons, representing 42 heart centers worldwide. According to the consensus statement [1], graft dysfunction (GD) has been classified into primary (PGD), in case of an unknown triggering factor or secondary (SGD) when a discernible cause such as hyper-acute rejection, pulmonary hypertension, or known surgical complications [1] can be identified. The diagnosis of GD is to be made within 24 h after completion of heart transplantation (Htx) surgery and a severity scale for GD should include mild, moderate, or severe grades based on specified criteria. Risks are often multifactorial and usually include donor, recipient, and surgical variables. Before the advent of short-term ventricular assist devices (VADs) and extra-corporeal membrane oxygenation (ECMO) support after transplant, severe EGF was likely considered to be fatal. Currently, the use of mechanical circulatory support (MCS) devices as treatment of GD is more widely well accepted and adopted whenever maximal medical management is not sufficient to support the newly transplanted graft. In this chapter, we will focus on actual indications, surgical strategies, and future perspectives of veno-arterial ECMO as a bridge to graft recovery in both pediatric and adult populations.

## 2. Clinical background and epidemiology

The exact incidence of PGD has been unknown until 2013 due to the lack of standardization of diagnostic criteria according to the historical observational studies as stated by the above mentioned ISHLT consensus paper [1]. However, the ISHLT registry data always offered specific information concerning epidemiology and clinical characteristics of PGD by time. The examination of early mortality after heart transplant documented in the registry shows that 66% of the death that occurs in the first 30 days after transplant are due to “graft failure” and “multi-organ dysfunction” [1]. Most of these events are probably the result of fatal PGD. An analysis of the United Network for Organ Sharing (UNOS) database was conducted for transplants occurring from 1999 to 2007 (n = 16,716) [3]. For this analysis, PGD was defined by “hard outcomes,” meaning postoperative death or retransplant, where the incidence of PGD was 2.5%. In this PGD group, 85% were due to deaths and 15% were due to retransplants [3]. A closer look at early mortality from the ISHLT revealed that more than 100,000 patients who received Htx between 1982 and 2011 shows that approximately 10% of patients dies within 30 days of transplant, and this number increases to 14% after 90 days [1]. The risk of 30-day and 90-day mortality was the highest in retransplant (18% and 22%) and congenital heart disease (17% and 21%), intermediate in valvular cardiomyopathy (14% and 18%), and the

lowest in ischemic (10% and 14%) and non-ischemic (8% and 12%) cardiomyopathy patients [1]. Increasing recipient age is a known risk factor associated with intermediate-term and long-term mortality after heart transplant; however, 30-day and 90-day mortality varies little in patients of different age groups, including patients older than 70 years. Sizable majority of early post-transplant deaths likely results from PGD. The recent reduction of early post-transplant mortality might have resulted from lower incidence and/or better treatment of PGD. There are considerable differences in early post-transplant mortality in patients who receive transplants for different heart disease etiologies, and early post-transplant mortality continues to represent a significant problem despite better survival. Concerning epidemiological data of Htx in children a retrospective review showing ECMO need in the early post-transplant period at Denver Children's Hospital, Aurora, Colorado. From 1990 to 2007, 310 children underwent Htx, and 28 children who underwent transplantation (9%) were placed on ECMO for postoperative primary graft failure [4]. They conclude that primary graft failure requiring mechanical circulatory support in the early period after transplantation is not uncommon in children (9%), and a long ischemic time is a major risk factor of graft dysfunction [4]. Pediatric cardiac allografts can be successfully salvaged by ECMO in a reasonable proportion of patients (54%) [4].

## 2.1. Pathogenesis

The transplant process may lead to donor heart graft several kinds of insults due to:

- Brain death and its sequelae in the donor.
- Hypothermic ischemia during transport.
- Warm ischemia during implant surgery.
- Reperfusion injury after release of the aortic cross-clamp in the recipient.

Systemic factors in the recipient determine a “hostile” environment that further compromises donor heart function after reperfusion. Associated with brain death in the donor, there is a series of events that result in impaired myocardial contractility and sensitize the heart to ischemia-reperfusion injury. An example is the intense release of myocardial norepinephrine immediately after brain death that causes cytosolic and mitochondrial calcium overload [5]. Mitochondrial calcium overload may activate autophagy, apoptosis, or necrosis [6]. During donor resuscitation, administration of exogenous catecholamines may determine a reduction of myocardial  $\beta$ -receptor sensitivity and an activation of multiple pro-inflammatory mediators, including complement [7–9]. Referring to hypothermic ischemia, during transport most donor hearts are stored in a cold preservation solution and transported on ice. Hypothermia slows but does not stop cellular metabolism, so progressive ischemic injury is an inevitable consequence of prolonged static storage. In addition, the absence of normal aerobic metabolism arrests the activity of transmembrane  $\text{Na}^+/\text{K}^+$  adenosinetriphosphatase pump consequently the switch to anaerobic metabolism during cold storage causes a rapid decline in high-energy phosphates and development of lactic acidosis [10].  $\text{Na}^+/\text{H}^+$  exchanger is activated by intracellular acidosis and it exchanges  $\text{H}^+$  for  $\text{Na}^+$  across the cell membrane. The increasing of intracellular  $\text{Na}^+$  determines an accu-

Donor risk factors	Recipient risk factors	Surgical procedural risk factors
• Age	• Age	• Ischemia time
• Cause of death	• Weight	• Donor-recipient mismatch
• Trauma	• Mechanical support	• Weight mismatch
• Cardiac dysfunction	• Congenital heart disease	• Experience of procurement team and center volume
• Inotropic support	• Multiple reoperation	• Cardioplegic solution
• Comorbidities: (diabetes, hypertension)	• LVAD explant	• Increased blood transfusion
• Drug abuse	• Comorbidities: (renal/liver dysfunction)	• Elective vs. emergency transplant
• LV hypertrophy	• Ventilator dependent	
• Valvular disease	• Multiorgan transplant	
• Hormone treatment	• Elevated PVR	
• CAD	• Allosensitization	
• Sepsis	• Infection	
• Troponin trend	• Retransplant	
• Hypernatremia		

**Table 1.** Risk factors for EGF.

mulation of intracellular  $\text{Ca}^{2+}$  by activation of the  $\text{Na}^+/\text{Ca}^+$  exchanger [11]. Other factors, recipient related, contribute to early graft dysfunction. It is possible to find two clinical conditions. The first is the presence of a high pulmonary vascular resistance in the recipient [12, 13]. In this case, the graft failure is considered secondary (to a known recipient factor) rather than primary. However, even with recipient pulmonary pressures and resistances within the accepted ranges for heart transplantation, a lower degree of pulmonary hypertension correlates with a lower incidence of PGD. The second scenario is characterized by activation of the systemic inflammatory response in the recipient, which causes vasodilated systemic circulation that is not responsive to medical therapy [14]. This “vasoplegic” response is associated with risks factors such as mechanical circulatory support before transplantation, large transfusion requirements, and prolonged cross-clamp time. In this circumstance, the “hostile environment” of the recipient results in PGD. The pathophysiology of PGD in this setting is not so clear, but it could involve the multiple action of many pro-inflammatory cytokines leading to upregulation of inducible nitric oxide synthase or indoleamine dioxygenase, with overproduction of nitric oxide or other endogenous vasodilators [14, 15]. The multiple risk factors for PGD include not only donor and perioperative factors but also recipient characteristics, confirming the multifaceted nature

of PGD. The risk factors (**Table 1**) for PGD related to recipient are: age, parameters reflecting pulmonary hypertension and more severe pre-transplant condition, including dependence on intravenous inotropic support, mechanical support and mechanical ventilation. Donor factors include age, female donor, and cause of brain death. Procedural factors are represented by ischemic time and donor-to-recipient weight mismatch. The RADIAL score (**Table 2**) is today the only validated scoring system for the prediction of PGD [16]. This predictive model was obtained after multivariate analysis of independent risk factors for PGD in a single-center derivation cohort of 621 heart transplants performed from 1984 to 2006. Six factors with similar influence were chosen to form the acronym RADIAL: four of these are related to the recipient: right atrial pressure (4–10 mmHg), age (4–60 years), diabetes and inotropic support dependence; and two are associated with the donor: age (4–30 years) and length of ischemia time (4–240 min). The presence of each of these factors in an individual patient adds one point to the final score. According to the RADIAL model, there are three groups with low (0–1 points), medium (2 points), and high (>3 points) risk for PGD.

<b>R (recipient)</b>	<b>Right atrial pressure</b>	<b>&gt;10 mmHg</b>	<b>1</b>
<b>A (recipient)</b>	Age	>60 years	1
<b>D (recipient)</b>	Diabetes	Diagnosis/treatment	1
<b>I (recipient)</b>	Inotropic support dependence		1
<b>A (recipient)</b>	Age	>30 years	1
<b>L (recipient)</b>	Length of ischemia	>240 min	1
Low risk for PGD		<b>(0–1) points</b>	
Medium risk for PGD		(2) points	
High risk for PGD		(>3) points	

**Table 2.** Radial score.

## 2.2. Classification

According to the consensus statement [1], graft dysfunction should be classified into PGD or secondary graft dysfunction (SGD) where there is a discernible cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications (e.g., uncontrolled bleeding; **Table 3**). It is necessary to make the diagnosis of PGD within 24 h after completion of the cardiac transplant surgery. There is an important difference between treatment of patients with RV failure and LV failure, so it was decided to divide PGD into two entities: PGD-LV, which includes LV and biventricular failure, and PGD-RV alone (**Table 3**). Finally, it was created a grading system for PGD-LV, which includes the descriptors of mild, moderate, and severe dysfunction. These were carefully defined with the use of hemodynamic variables, echocardiography results, level of inotropic support, and need for mechanical circulatory support. Because RV failure can often be more difficult to quantify, there are no grades for the severity of PGD-RV.

Primary graft dysfunction (PGD)	Secondary graft dysfunction
a. PGD-left ventricle (PGD-LV): includes [21] left and biventricular dysfunction	Occurs when there is a discernible cause for graft dysfunction (e.g., hyperacute rejection, pulmonary hypertension, known surgical complication)
b. PGD-right ventricle (PGD-RV): includes right ventricular dysfunction alone	
PGD-left ventricle (PGDLV):	<p><i>Mild PGD-LV: one of the following criteria must be met</i> LVEF &lt; 40% by echocardiography, or hemodynamics with RAP &gt; 15 mmHg, PCWP &gt; 20 mmHg, CI &lt; 2.0 L/min/m<sup>2</sup> (lasting more than 1 h) requiring low-dose inotropes</p> <p><i>Moderate PGD-LV: must meet one criterion from I and another criterion from II:</i> I. One criteria from the following: left ventricular ejection fraction &lt; 40%, or hemodynamic compromise with RAP &gt; 15 mmHg, PCWP &gt; 20 mmHg, CI &lt; 2.0 L/min/m<sup>2</sup>, hypotension with MAP &lt; 70 mmHg (lasting more than 1 h). II. One criteria from the following: *High-dose inotropes – Inotrope score &gt; 10<sup>a</sup> or **Newly placed IABP (regardless of inotropes)</p> <p><i>Severe PGD-LV</i> Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP</p>
PGD-right ventricle (PGDRV):	<p><i>Diagnosis requires either both I and II, or III alone:</i> I. Hemodynamics with RAP &gt; 15 mmHg, PCWP &lt; 15 mmHg, CI &lt; 2.0 L/min/m<sup>2</sup> II. TPG &lt; 15 mmHg and/or pulmonary artery systolic pressure &lt; 50 mmHg, or III. Need for RVAD</p>

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.

<sup>a</sup>Inotrope score = dopamine(x1) + dobutamine(x1) + amrinone(x1) + milrinone(x15) + epinephrine(x100) + norepinephrine(x100) with each drug dosed in µg/kg/min [k2].

**Table 3.** Classification of graft dysfunction.

### 2.3. Pharmacologic and mechanical management

Before the introduction of short-term VAD support and ECMO after Htx, PGD was frequently fatal except for that cases where emergency salvage retransplantation was possible. D'Alessandro et al. from La Pitié-Salpêtrière in Paris retrospectively evaluated the use of ECMO temporary support as a treatment for PGD [17]. They studied 394 patients, who underwent cardiac transplant between 2000 and 2006. In 90 patients, PGD after transplant occurred. In this study, PGD was defined as the need for inotrope support with epinephrine and/or the

necessity for mechanical circulatory support in the postoperative 48 h. Of these 90 patients, 54 received ECMO, 8 used other assist devices, and 28 were treated only with maximal inotropes [17]. Of those medically treated (i.e., on maximal inotropes only), survival was 46% compared with a survival of 50% for those on ECMO [17]. These data confirm that ECMO is becoming a safer and more effective technique to manage patients with PGD. A retrospective analysis of short-term VAD use after transplantation found that in 38 patients from 2003 to 2008 who have been implanted with the CentriMag device (Levitronix, Waltham, MA) for PGD survival was 50% at 30 days and 32% at 1 year [18]. Earlier implantation of the device after transplant seemed to correlate with improved survival, and all survivors were supported with the device for no more than 30 days [18]. In summary, medical treatment of PGD consists of inotrope and vasodilator support and these are considered the first line therapy for PGD and may be helpful for milder cases of PGD. ECMO and other mechanical circulatory support are the only effective options for more severe cases, appearing to reduce mortality compared with other treatments. From the data, early intervention and short-term support appears to be associated with improved survival.

### 3. Indication of ECMO in EGF

EGF is the main cause of early mortality after transplantation. Hemodynamic deterioration caused by cardiogenic shock due to the pump failure unresponsive to inotropes has a catastrophic progression if not corrected in time [2]. As the pathophysiology of EGF is often unclear, specific treatment remains still challenging and the choice of the most suitable support option (e.g., ventricular assist device [VAD] or extracorporeal membrane oxygenation [ECMO]) remains controversial. In particular, ECMO support, even if associated with mortality and a high rate of morbidity (such as bleeding, ischemic or thromboembolic events and infections), is considered a valid therapeutic route [19, 20].

#### 3.1. Adult population

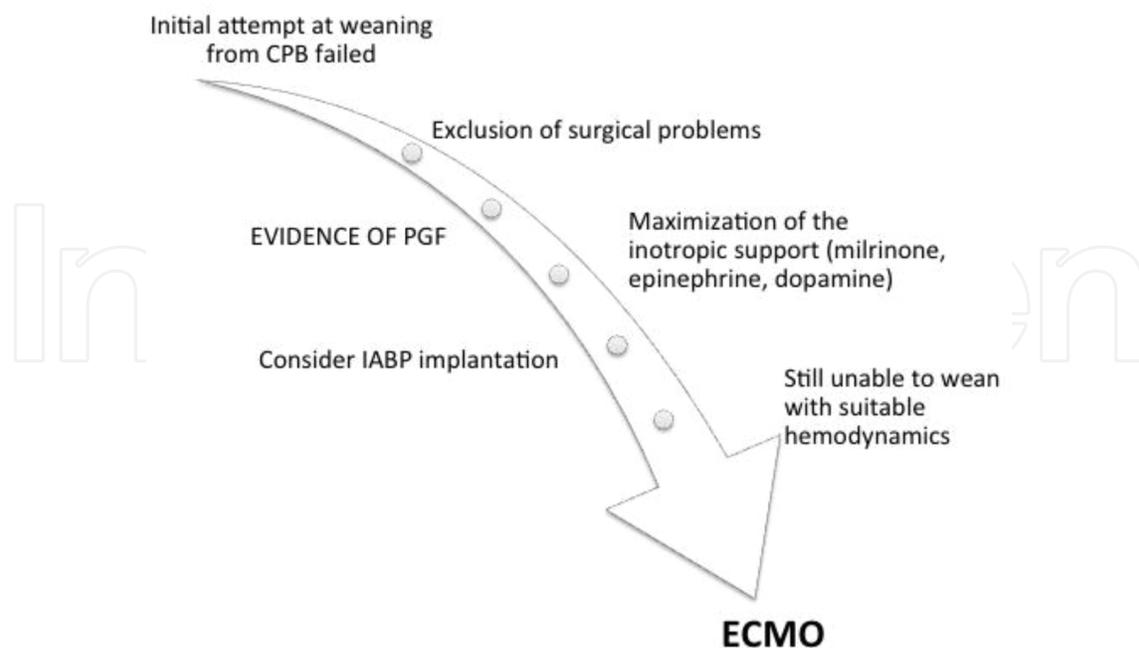
Actually, there is not a real or unique indication for ECMO implanting in case of EGF. What we can consider are the single centers experience. Routinely, after exclusion of surgical problems, the first line treatment starts using inotropic drugs such as milrinone, epinephrine, and dopamine. In case of hard weaning from CPB machine because of unstable hemodynamics should be considered the use of intra-aortic balloon pump (IABP) and prepare the patient for ECMO implantation (**Figure 1**). In the Cedars-Sinai Heart Institute, for example, they place on ECMO if cardiac index remains  $<2.5 \text{ L/min/m}^2$  with central venous pressure and left atrial pressure  $>12 \text{ mmHg}$  and a mean arterial pressure  $<65 \text{ mmHg}$ . The approach of the Columbia University at the management of PGD has evolved: most patients now receive BiVAD support, usually a C-Mag BiVAD with left apical cannulation. More recently ventricular-arterial ECMO has also become a more common mode of support. The median length of device support at their transplant center was 7 days, with an in-hospital mortality of 51%. Only 5.7% survived to re-transplantation [1].

### 3.2. Pediatric population

ECMO represents the most commonly used method of mechanical circulatory support in the post-transplantation period of pediatric patients [21]. In the same way of the adult, also for the pediatric population, the indications for the ECMO implantation are not clear. In almost all centers, the extracorporeal membrane oxygenation is started in the operating room because of the inability to wean from cardiopulmonary bypass, and only a few cases required ECMO in the first 48 h after transplantation requiring a cannulation in the cardiac intensive care unit [4]. In particular, as reported by Tissot et al. [4], the timing of ECMO cannulation is not predictive of outcome. In their population, in fact, the survival is not significantly different between patients started on ECMO in the operating room with those cannulated in the first 48 h after transplantation for hemodynamic instability or cardiac arrest in the cardiac intensive care unit. This is in contrast with Galantowicz et al. [22], who reported no chance of survival if the cardiac allograft could not support the patient after cardiopulmonary bypass.

## 4. Surgical approach

Mechanical circulatory support has evolved markedly over recent years even in terms of surgical techniques. In particular, ECMO support can be deployed peripherally or centrally, using a traditional or minimally-invasive approach. There is still a great debate about the cannulation site strategies (**Table 1**). The central cannulation has several advantages such as full antegrade outflow and avoidance of peripheral ischemic complications [23]. However, it



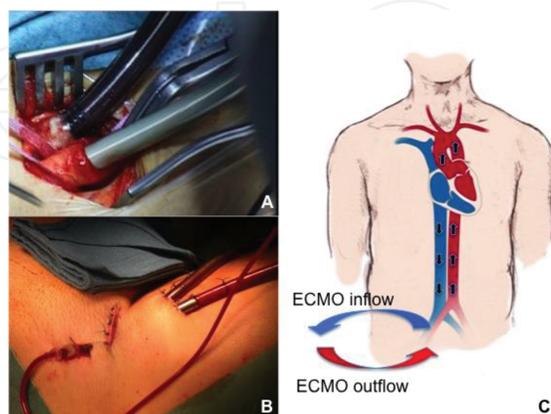
**Figure 1.** Decision algorithm for ECMO implantation for EGF.

leads to an high risk for bleeding, tamponade, and infection [24]. These are the main reasons why a lot of centers adopt a peripheral setting.

#### 4.1. Peripheral cannulation

For veno-arterial ECMO installation, a femoral vein and a femoral artery are usually used for vascular access. The correct position of the venous cannula tip is the mid-right atrium to have an homogenous drainage of venous blood from both caval veins. The femoral arterial cannula should be fully introduced till its tip reaches the common iliac artery, in adults (**Figure 2**). Commonly, in our center, we use a DLP Biomedicus 15–19 Fr (Medtronic Inc., Minneapolis, MN) cannula for the femoral artery, and a DLP Biomedicus 17–23 Fr (Medtronic Inc.) cannula inserted into the femoral vein for the venous drainage [25]. Both insertions are performed using the Seldinger technique after anterior vessel wall exposure and secured with pledgeted, reinforced purse string prolene sutures. Combined IABP support is additionally adopted in the peripheral ECMO population to indirectly “vent” the left ventricle and avoids the pulmonary edema. For peripheral cannulation, a continuous-wave Doppler image of the tibial artery flow and pulsatility should be acquired every 2 days, in the presence of a consultant vascular surgeon, to evaluate and provide a correct distal leg perfusion.

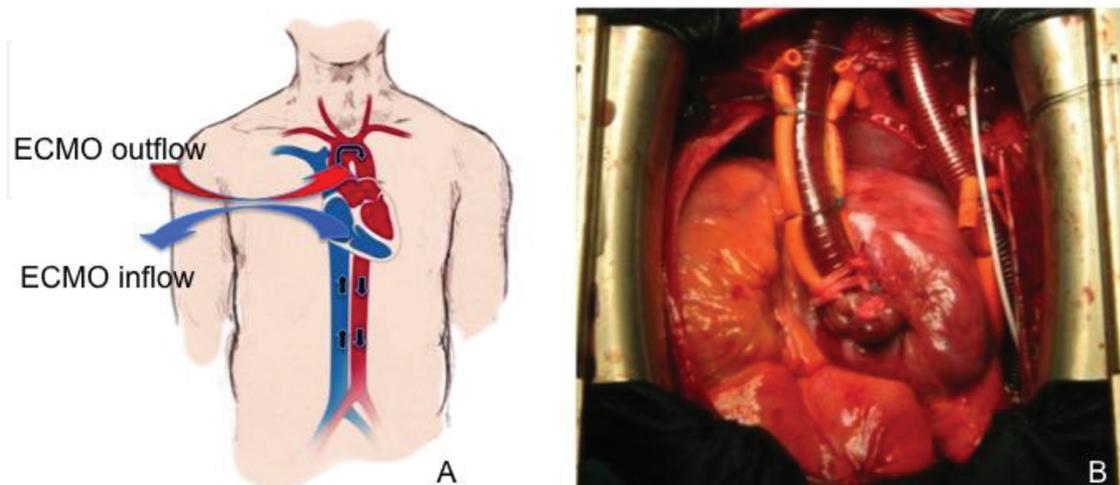
Although, as described above, the peripheral cannulation reduces the risk of bleeding and of infection, it can lead to important lower limb ischemia and the so-called “watershed phenomenon.” The “native” flow meet the retrograde blood flow from the arterial cannula somewhere between the ascending aorta and the renal arteries at a point called the “watershed.” All areas distal to this zone received blood oxygenated by the ECMO; meanwhile, the upper part receives blood from the left ventricle depending on respiratory function of the lung which can be severely compromised [26]. In an effort to minimize these matters, some centers reported on the use of a side graft sutured on the axillary artery as arterial return for ECMO peripheral setting. The advantages include: a low grade of atherosclerosis vessel disease, an antegrade flow into the aorta, and a preferential delivery of oxygenated blood into the heart and brain [27].



**Figure 2.** Peripheral ECMO setting (A: intra-operative direct cannulation; B: intra-operative percutaneous approach; C: setting).

## 4.2. Central cannulation

The easiest way to perform a central approach for ECMO implantation after Htx is to re-utilize the cannulas adopted for aortic arterial return and atrial venous drainage during the cardiopulmonary bypass (CPB). Usually, the aortic cannula is left in situ to avoid new aortic puncturing, while the venous cannula is placed into the right atrium through its lateral wall. At our center, the central cannulation is performed using the right atrium, through its lateral wall as access, and the left atrium, between the right pulmonary veins as access, for venous drainage [25]. The employed cannulae are two 28-Fr wire-reinforced angled veno-atrial cannula (Jostra Venous Catheter OD; Maquet Cardiopulmonary AG, Hirrlingen, Germany) for both atria. The outflow cannula is always positioned into the ascending aorta [straight aortic perfusion cannula (22 or 24 Fr); Edwards Lifesciences LLC, Irvine, CA]. All cannulas are secured with pledgeted, reinforced purse string prolene sutures, tunneled through sub-costal incisions to allow chest closure, and then connected to the circuit, avoiding air in the system. In case of graft isolated right ventricular failure (RVF) and pre-transplant recipient severe pulmonary hypertension, the extracorporeal right-to-left atrium bypass (ECRLAB) ECMO setting may be adopted (**Figure 3**) [25]. Briefly, the cannulation is performed centrally, using the right atrium for venous drainage and the left atrium, between the right pulmonary veins, for arterial return. The cannulae are two 28-Fr wire-reinforced angled veno-atrial cannula (Maquet) for both atria. The conventional circuits, with the inflow cannula in the right atrium and the outflow cannula in the pulmonary artery, could not completely decompress the right heart in case of high pulmonary arterial pressures, presumably because no blood entering the chamber can be ejected across the pulmonary valve. ECRLAB improves the right-sided pressures, showing that the component of the right ventricular afterload is “reversible” [25]. ECRLAB appears as well, by increasing both cardiac output and return to the left atrium and ventricle, to improve end organ function avoiding any eventual multiple organ failure syndrome (MOF).



**Figure 3.** Central ECMO setting (A: setting; B: intra-operative picture).

### 4.3. Minimally invasive

A challenging option to reduce the ECMO-related risk of complications is the adoption of minimally invasive surgical approaches. There are few reports in the literature. In a recent paper, Weymann et al. describe their technique [28]. After a small right-sided thoracotomy at the eighth intercostal space, flexible arterial and venous cannulas are tunneled. A sewing ring is secured to the right atrium and a tube graft is anastomosed to the ascending aorta. Following full-dose heparinization, the arterial cannula is inserted with the tip into the vascular graft for the ascending aorta and the venous cannula via the ring into the right atrium. After de-airing, the central extracorporeal life support is set at full flow. So far, this surgical approach has not been described in patients who underwent ECMO implantation as treatment of early graft failure, but it might be considered a valid idea for future implantations.

## 5. Weaning protocol

There are no standardized methods or techniques with regards to weaning ECMO. Usually, the factors indicating cardiac recovery, and so the possibility of weaning from the ECMO, are: increasing blood pressure, falling central venous and/or pulmonary pressures, and improving of cardiac contraction [23]. It is so useful reassess the myocardial function every 24/48 h with TTE, trans-thoracic echocardiography / TEE, trans-esophageal echocardiography in addition to daily hemodynamics. It would be reasonable to reduce pump flows in 0.5 L decrements to 2 L/min over 36–48 h checking the above mentioned variables. The weaning protocols change from center to center according to the personal experience. Lima et al. [29], for example, routinely use the intra-aortic balloon pump for ECMO weaning. At our institution, full ECMO flow is instituted for at least 72 h [25]. Criteria for weaning include an  $SvO_2 \geq 70\%$ , a hematocrit of 28–30%, the absence of bleeding or tamponade, the absence of left heart distension, improvement in contraction of both ventricles, normal blood lactate levels ( $<1.5$  mmol/L), and a normal urine output ( $>80$  mL/h). A gradual weaning by reducing the ECMO flow by 10% every ~12 h is our main strategy, together with close TEE and Swan-Ganz catheter examinations. Once an ECMO flow of 1.5 L/min/m<sup>2</sup> is reached, in the presence of two or more consultant surgeons, the pump flow is radically reduced at 0.5 L/min/m<sup>2</sup> for ~30 min. If the hemodynamics in terms of systemic arterial pressure (mean pressure  $>60$  mmHg), LV contractility (EF  $>40\%$ ), aortic blood flow time-velocity integral  $>10$  cm, central venous pressure (10–12 mmHg), wedge pressure (10–12 mmHg) and  $SvO_2$  ( $>70\%$ ) show no significant changes without the addition of new inotropes, the heparin is stopped, and ECMO support is removed in the operating room within the next 3 h [25].

## 6. Outcomes

In case of primary graft failure, when all pharmacological options fail, ECMO system represents surely a good option in cardiac surgeon's hands to secure a valid circulatory

support. Outcomes in both subtypes, adult and pediatric population, vary among the different centers (**Table 4**). This may be related to several aspects such as the time of implantation and surgical techniques.

Transplantation center	Year	ECMO in PGF/ total cardiac transplants	Surgical approach
Cedars-Sinai Heart Institute [1]	2005–2012	8/555	–Central cannulation: 100% –Peripheral cannulation: 0
Instituto de Cardiologia do Distrito Federal, Brasília [29]	2007–2013	11/71	–Central cannulation: 81.8% –Peripheral cannulation: 18.2%
Heart Center Leipzig [35]	1997–2011	28/298	–Central cannulation: 0 –Peripheral cannulation: 100%
Cardiac surgery and Heart Transplant Unit (ISMETT), Palermo [30]	2006–2013	18/114	–Central cannulation: 77.8% –Peripheral cannulation: 16.7% –Central arterial cannulation and peripheral venous cannulation: 5.5%
Cleveland Clinic [36]	1990–2009	43/1417	–Central cannulation: 0 –Peripheral cannulation: 100%
The Alfred Hospital, Melbourne [37]	2000–2009	39/239	–Central cannulation: 66.6% –Peripheral cannulation: 41%
Groupe hospitalier Pitié-Salpêtrière [17]	2000–2006	54/394	–Central cannulation: 48.1% –Peripheral cannulation: 51.9%
S. Orsola-Malpighi Hospital [38]	2002–2007	11/188	–Central cannulation: 54.6% –Peripheral cannulation: 45.4%

**Table 4.** Outcomes of ECMO support as treatment of EGF.

### 6.1. Adult

In literature, the successful ECMO weaning rate ranges from 68% to 82% and corresponds to a hospital mortality rate of 50%. In the experience reported by Santise et al. [30], 13 patients (72.2%—13/18) were weaned from the mechanical circulatory support, and eight of them (44%) were discharged home. The causes of death of the patients weaned from ECMO were multi-organ failure, sepsis and acute mycotic rupture of pulmonary artery. Also the group of La Pitié-Salpêtrière [17], in an older paper, report good results after ECMO implantation. Among the 54 patients supported with ECMO, 36 were weaned from the assistance and 27 were discharged. In this study, patients treated with ECMO had the same 1-year conditional survival as patients not having suffered EGF: 94% at 3 years.

## 6.2. Pediatric

Early primary graft failure after Htx in children is associated with significant rates of mortality and morbidity. Extracorporeal membrane oxygenation is widely used and is well established to support circulatory function in children with post-cardiotomy low cardiac output syndrome [31]. The manuscript with the largest series on pediatric heart transplantation is that of Tissot from Denver Children's Hospital, Aurora, Colorado [4]. They retrospectively analyzed the indications and outcome of extracorporeal membrane oxygenation for early primary graft failure and determined its impact on long-term graft function and rejection risk. From 1990 to 2007, 28 (9%) of 310 children who underwent transplantation for cardiomyopathy or congenital heart disease required ECMO support. Fifteen children were successfully weaned off ECMO and discharged alive (54%). This is comparable to what has been previously reported in the pediatric population [21, 32, 33].

Mean duration of ECMO was 2.8 days for survivors (median 3 days) compared with 4.8 days for non-survivors (median 5 days). The duration of cannulation was so important in this series, with no child surviving ECMO support for >4 days. The long-term outcome in those patients supported by ECMO for primary graft failure and surviving to hospital discharge was excellent. There was, in fact, 100% 3-year survival in the ECMO survivor group, with 13 patients (46%) currently alive at a mean follow-up of  $8.1 \pm 3.8$  years.

## 7. Conclusions and perspectives

PGD is the main cause of early mortality after Htx. Hemodynamic deterioration caused by cardiogenic shock due to pump failure unresponsive to inotropes has a catastrophic progression if not solved in time. Early institution of ECMO allows myocardial graft function recovery despite multifactorial insults and prevents the development of an eventual multisystem organ failure which would otherwise occur in case of a prolonged period of uncorrected cardiogenic shock [34]. In addition to the short-term effects, it has been observed that ECMO implantation, as a bridge to graft recovery after transplantation, can be used without influencing the long-term outcome of this high-risk postoperative cohort of patients. Currently, we take advantage from a wide available range of surgical options for ECMO setting. However, we are still too far from the ideal mechanical support device as routine and well-accepted treatment strategy.

## Acknowledgements

**Disclosures:** None.

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