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Mechanical Circulatory Support (MCS) for Primary Graft Dysfunction (PGD)

Luiz Fernando Caneo and Vitor Barzilai

Additional information is available at the end of the chapter

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Abstract

Primary graft dysfunction is the main cause of early mortality after heart transplantation (HT). Preventive strategies to avoid primary graft dysfunction (PGD) have been focused on better donor choice and maintenance, heart preservation methods in long-distance retrievals with prolonged ischemia time, and better myocardial protection during implantation, among others. Hemodynamic deterioration, caused by cardiogenic shock due to pump failure unresponsive to inotropes, has a catastrophic progression if not corrected in time. Severe PGD without response to inotropes and heart rhythm control in the absence of cardiac tamponade should be treated promptly with mechanical circulatory support. Extracorporeal life support (ECLS) should be installed early, before the occurrence of multiorgan dysfunction or prior to cardiac arrest, as highlighted in the literature. The aim of this chapter is to discuss the use of mechanical circulatory support (MCS) and its impact on the success to survival for patients with PGD.

Keywords: extracorporeal membrane oxygenation, mechanical circulatory support, primary graft dysfunction, orthotopic heart transplantation, heart failure, heart-assist devices

1. Introduction

Heart transplantation (HT) remains the preferred treatment for end-stage heart disease that currently affects 5.1 million people in the United States, with an estimated growth of 25% by 2030 [1]. More than 4000 patients undergo HT annually worldwide for this condition [2, 3], with an improved survival rate in the last two decades. Through the years, the advent of
multiple platforms of mechanical circulatory support (MCS) as an arm of transplantation has made it possible to rescue patients that were too sick to be treated without the help of devices.

Despite surgical advances and improved long-term survival, heart transplant patients are still at significant risk to develop early graft dysfunction (EGD), leading to significant perioperative morbidity and mortality [2, 4, 5]. Notwithstanding the better results of HT, mortality from EGD varies among centers and over the years. In addition, the different set of criteria jeopardize comparison for incidence and mortality.

There are two basic entities that compose of EGD: primary graft dysfunction (PGD) and secondary graft dysfunction (SGD). The latter is based on pathology-proven rejection, clear surgical complications, or hemodynamic parameters. A postoperative transpulmonary gradient greater than 15 mmHg, associated with low cardiac output, was considered as graft dysfunction secondary to pulmonary hypertension classified as SGD. The aim of this chapter is to discuss exclusively cardiogenic shock due to PGD and its management. Secondary graft dysfunction is not the scope of this chapter.

2. Primary graft dysfunction

2.1. Definitions and classification

Primary graft dysfunction is reported as dysfunction affecting the right ventricle (RV), left ventricle (LV), or both, according to echocardiographic findings. Primary graft dysfunction (PGD) is common and ranges from 2.3 to 28.2% depending on the definition [6–10].

The diagnosis of PGD should be considered if any dysfunction is observed at the end of cardiopulmonary bypass, restricted to the first 24 h after surgery and based on echocardiographic and/or hemodynamic criteria, as summarized in Table 1.

Severe PGD is defined as the need for MCS—other than an intra-aortic balloon pump—to maintain an adequate organ perfusion following HT and is the leading cause of early mortality after transplantation [5]. Hemodynamic deterioration caused by cardiogenic shock due to pump failure unresponsive to inotropes has a catastrophic progression if not addressed in time. For this reason, heart transplant patients should be routinely monitored by a pulmonary artery catheter. It provides continuous information about cardiac output and other real-time hemodynamics parameters required for therapeutic decision-making, in combination with other clinical variables, such as tissue perfusion. In a PGD after HT, the amount of inotropes and vasopressors—vasotropic score—the patient is on and micro- and macro-hemodynamics help to decide whether to rely on medical management or choose MCS.

Intraoperative transesophageal echocardiography (TEE) is recommended routinely upon the discontinuation of cardiopulmonary bypass. It provides useful information about ventricular dimensions and function, blood volume, residual surgical defects, and helps to de-air cavities. If the diagnosis of postoperative shock is challenging, both operating room (OR) and bedside echocardiography are informative and should be performed whenever cardiac dysfunction
and hemodynamic parameters indicate cardiogenic shock. Figure 1 shows a suggested algorithm to rule out PGD post-heart transplantation.

In a recent consensus on April 23, 2013, during the annual meeting of the International Society of Heart and Lung Transplantation (ISHLT) [5], PGD was defined as any graft dysfunction that occurs up to 24 h after transplantation. This agreement formulates guidelines to better define the diagnosis and management of patients with primary graft dysfunction (PGD) in heart transplantation. Before the conference, an online survey was used to obtain contemporary thoughts on diagnosis and management of PGD patients from transplant centers. A total of 47 transplant centers responded and the results are summarized in Table 1. Epidemiology factors were set as the baseline. Parameters such as the requirement of inotropic support, left ventricular ejection fraction (LVEF), and requirement of cardiac mechanical support were put as possible criteria for PGD. The purpose of this consensus was to initiate a standardization of the study of PGD and serve as a guide for the heart transplant community regarding diagnosis, management, and risk stratification of post-transplanted PGD, thus permitting uniform comparisons among centers and studies.

<table>
<thead>
<tr>
<th>Classification of primary graft dysfunction after heart transplantation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild - meets one of the following criteria:</td>
</tr>
<tr>
<td>Echocardiography: LVEF &lt; 40% OR</td>
</tr>
<tr>
<td>Hemodynamics: CVP &gt; 15 mmHg, PCWP &gt; 20 mmHg, CI &lt; 2 L/min/m2 lasting for 1 hour and requiring low-dose inotropes</td>
</tr>
<tr>
<td>PGD-LV Moderate - meets one criterion from 1 and another criterion from 2:</td>
</tr>
<tr>
<td>Hemodynamics: CVP &gt; 15 mmHg, PCWP &gt; 20 mmHg, CI &lt; 2 L/min/m2, hypotension with MAP &lt; 70 mmHg</td>
</tr>
<tr>
<td>2. Inotrope score &gt; 10 or intra-aortic balloon pump</td>
</tr>
<tr>
<td>Severe Dependence on mechanical circulatory support, excluding intra-aortic balloon pump</td>
</tr>
<tr>
<td>PGD-RV Requires 1 + 2, or 3 alone</td>
</tr>
<tr>
<td>2. TPG &lt; 15 mmHg AND/OR SBP &lt; 50 mmHg</td>
</tr>
<tr>
<td>3. Requirement of right circulatory assistance</td>
</tr>
</tbody>
</table>

PGD-LV: left ventricular primary graft dysfunction; LVEF: left ventricular ejection fraction; CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; MAP: mean arterial pressure; PGD-RV: right ventricular primary graft dysfunction; TPG: transpulmonary pressure gradient; SBP: systolic blood pressure.
The conference had 71 participants—including cardiologists, cardiac surgeons, pathologists, and immunologists—representing 42 heart transplant centers from North America, Australia, Europe, and Asia, that had published on PGD or had vast clinical experience in heart transplantation.

Additionally, the moment to start support is not well established. A high inotropic score seems to be related with worst prognosis. Beside high inotropic score, the need of vasotropic agents to sustain hemodynamics plays an important role in choice for ECLS in PGD. It is important to acknowledge that a vasoactive-inotropic score (Figure 2), rather only the inotropic score, may determine better the prognosis and initiation of support. In Cardiogenic shock patients, a high vasoactive-inotropic score during the first 48 hours was related with increased in-hospital mortality [11, 12].

<table>
<thead>
<tr>
<th>During implant</th>
</tr>
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<tbody>
<tr>
<td>Optimize protection during bypass:</td>
</tr>
<tr>
<td>Maximize myocardial protection during bypass according to the type of Cardioplegia</td>
</tr>
<tr>
<td>LV Venting to avoid rapidly rewarming</td>
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<tr>
<th>After implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimise inotropes before weaning</td>
</tr>
<tr>
<td>Rule out air in coronary arteries</td>
</tr>
<tr>
<td>Rule out Kinking of pulmonary arteries</td>
</tr>
<tr>
<td>Start Reperfusion at least 30 min before weaning bypass</td>
</tr>
<tr>
<td>If difficult to wean bypass, extends reperfusion.</td>
</tr>
<tr>
<td>Exclude RV disfunction after increased PVR</td>
</tr>
</tbody>
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<tr>
<th>End of bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable to wean bypass, higher vasoactive-inotropic score:</td>
</tr>
<tr>
<td>Consider PGD</td>
</tr>
<tr>
<td>Consider IABP, prepare for MCS/ECLS.</td>
</tr>
<tr>
<td>Consider a myocardial biopsy sample</td>
</tr>
</tbody>
</table>

Figure 1. Ruling out secondary graft dysfunction in heart transplantation.
2.2. Etiology and Pathogenesis

The etiology of PGD is likely to be multifactorial. Donor, procedure, and recipient causes are involved. Brain death and its sequelae in the donor, hypothermic ischemia during transport, warm ischemia during implant surgery, and reperfusion injury after the release of the aortic cross-clamp in the recipient can negatively affect the donor's heart. In addition, systemic factors in the recipient may create a "hostile" environment that further compromises its function after reperfusion and contributes to the development of PGD.

It is important to say that PDG is a phenomenon not correlated with hyperacute rejection. The results of the International Society of Heart and Lung Transplantation (ISHLT) autopsy survey pre-consensus showed that less than 4% of biopsies had some kind of antibody-mediated rejection and 7% had evidence of cellular rejection [5].

2.2.1. Donor aspects

Donor's brain death is associated with a series of events that result in impaired myocardial contractility and sensitize the heart to ischemia–reperfusion injury [13]. These events include an intense release of endogenous norepinephrine that results in mitochondrial and cytosolic calcium overload that may activate autophagy, apoptosis, or necrosis. Calcium overload of the contractile proteins leads to contracture and is associated with a characteristic histologic appearance known as "contraction band necrosis." Administration of exogenous catecholamines during donor resuscitation may contribute to desensitization of myocardial β-receptor signaling after brain death. Many other donor-related aspects leading to PGD are described, including ischemic preconditioning insults related to older donors [14].

Most donor hearts are transported and stored in a cold preservation solution and that slows but does not effectively arrest cellular metabolism. Consequently, a progressive ischemic injury is an inevitable consequence of prolonged static storage.

Furthermore, the reperfusion of the heart with oxygenated blood leads to further calcium overload and an initial burst of oxygen-derived free radicals that bind to and disrupt the function of multiple cellular enzymes. The combination of Ca⁺ overload and high oxidant stress in an energy-depleted cardiac myocyte activates the formation of the mitochondrial permeability transition pore (MPTP)—a non-specific channel that forms in the mitochondrial membrane allowing pro-apoptotic factors, such as cytochrome C, to be released into the cell cytoplasm [15]. Water that enters by the MPTP causes mitochondrial swelling and may lead to membrane rupture, triggering necrotic cell death. Currently, there is an increasing interest...
in ex-vivo perfusion of the donor’s heart in order to preserve the organ, minimize the above-mentioned negative impact of preimplantation ischemia, and increase availability [16].

2.2.2. Recipient aspects

Vasoplegia has a catastrophic result on any heart surgery, particularly in heart transplant, in which it seems to affect the donor’s heart impairing its ability to adapt to this hostile environment. Many aspects of the receptor are involved in the genesis of this phenomenon. Risk factors include mechanical circulatory support before transplantation, prolonged cross-clamp time, and significant transfusion requirements. The activation of systemic inflammatory response in the recipient results in a vasodilated systemic circulation that is refractory to conventional vasopressor support that seems to lead to PGD. It probably involves the concerted action of multiple pro-inflammatory cytokines leading to upregulation of inducible nitric oxide synthase or indoleamine dioxygenase, with overproduction of nitric oxide or other endogenous vasodilators.

2.3. Risk factors

Transplanted hearts are at risk of ischemia/reperfusion injury, damage from proinflammatory cytokines, and beats on decreased donor cortisol and thyroid hormone levels [17–21]. Recipient-related factors include age, increased pulmonary vascular resistance (PVR), and recipient inflammatory cytokines, which can worsen vasoplegia, as well as oxidative stress in the transplanted heart [22–30]. In addition, transplant recipient dependence on pre-transplantation inotropic support and mechanical ventilation has been associated with increased incidence of PGD [24, 31–34].

In a single-center study, Segovia et al. [26] developed a predictive model for the development of PGD. The risk factors were included in the model and used to calculate a predictive score are recipient age ≥ 60 years, recipient diabetes mellitus, recipient inotrope dependence, right atrial pressure ≥ 10 mm Hg, donor age ≥ 30 years, and ischemic time ≥ 4 h (RADIAL score) [26]. This model was later validated in a separate cohort of HT performed at programs in Spain between 2006 and 2010 [35]. In the latter study, PGD occurred with an incidence of 22%. Isolated RV dysfunction was present in 45% of patients with PGD, whereas isolated LV PGD occurred in 8% of patients and combined biventricular PGD in 47%. The RADIAL score was higher in patients with PGD and stratified patients into groups with incremental PGD incidence [35].

Nicoara et al. [36] conducted a single-center retrospective cohort study to evaluate the incidence, trends, and independently associated risk factors for PGD after HT. In addition, they explored the performance of the RADIAL score variables in this study population. Of the 317 patients who underwent HT over the study period and met inclusion criteria, 99 (31.23%) developed PGD defined according to the ISHLT consensus statement [5]. Isolated PGD-LV occurred in 60 patients (18.9%), 22 patients (7%) had biventricular PGD and 17 patients (5.3%) had isolated PGD-RV. Risk factors independently associated with the type of PGD included ischemia time, recipient African American race, and recipient pre-transplantation treatment with amiodarone [36].
Several studies previously identified a variety of donor, recipient, and procedural risk factors associated with PGD, with a high variability of results giving different definitions, use of single-center or multi-center databases, and different time periods analyzed [37, 38–41]. Most consistently among these are donor age [22], donor high dose of inotropic support [24], cause of brain death [24], recipient age [24, 36], recipient inotropic support [26], mechanical support [22, 24], ischemia time [24, 36], and donor-recipient weight mismatches [32]. Several studies [36–37, 42] identified ischemia time as an independent risk factor associated with PGD development, with each additional hour of ischemia time almost doubling the risk of PGD.

2.3.1. Amiodarone use

Recipient treatment with amiodarone pre-transplantation has been controversially discussed, with divergent results regarding early graft failure, morbidity, and mortality after heart transplantation [43–46]. Nicoara et al. [36] found that recipient pre-transplantation’s use of amiodarone was an independent factor that increases the risk of PGD development, by 67%. The 30-s official adult heart transplantation report from the registry of ISHLT did not find amiodarone independently associated with early graft failure. However, we had a higher incidence of early graft failure and in-hospital graft dysfunction among patients treated with amiodarone, suggesting that it may play a role in early post-transplantation outcomes or may be associated with an unmeasured indicator an ill patient population [3]. A recent retrospective cohort analysis of adult HT recipients from the ISHLT registry found that amiodarone use before HT has increased over time and is associated with increased 1-year mortality [46]. The long half life of amiodarone combined with its pharmacological effects—negative chronotropic and inotropic, calcium channel blockage, and α- and β-receptor blockade—may be responsible for its effects or an unidentified interaction with oxidative stress leading to worsening ischemia–reperfusion injury, but this is speculative [46].

2.3.2. Congenital heart disease

Over the last decade, the advances in the medical and surgical management of patients with congenital heart disease (CHD) have led to an improvement in their life expectancy with 85% of children surviving till adulthood [47]. However, some patients will develop late myocardial dysfunction resulting in heart failure with 10–20% of them requiring heart transplantation [48, 49]. Adults with congenital heart diseases recipients (ACHDR) pose unique challenges due to complex anatomy, multiple prior procedures, preformed human leucocyte antigen (HLA) antibodies, pulmonary hypertension, and malnutrition [50]. Because of these complexities, ACHDR has a higher operative [51, 52] and a 1-year mortality [2, 53].

In ACHDR, graft dysfunction was seen more commonly when compared to non-cardiac recipients (NCR) (9.9% vs. 7.4%, p < 0.01).

United Network for Organ Sharing (UNOS) database reports three categories of graft dysfunction: primary non-function, that is, primary graft dysfunction (PGD), acute rejection, and chronic rejection. PGD was significantly higher in ACHDR compared to NCR (4.3% vs. 2.6%, p < 0.01); however, there was no difference in acute and chronic rejection rates [49]. PGD continues to be a significant cause of morbidity in the most recent era [54].
Graft and cardiovascular dysfunction in ACHDR were the top two causes of early mortality and most likely related to the presence of elevated PVR, allosensitization, and longer donor organ ischemic times [30, 55–59]. The ACHDR were more likely to have longer-than-4-h ischemic times, peak panel-reactive antibody (PRA) class II >10%, and were found to have a higher rate of graft failure due to primary graft dysfunction. Thompson et al. showed that early graft survival was directly related to the number of HLA-DR (class-II) mismatches [59].

Graft dysfunction and postoperative bleeding are more likely to cause death in ACHDR compared to non-cardiac recipients (NCR) [49, 53, 60]. Because of graft dysfunction and young age, the re-transplant rate is higher among ACHDR compared to NCR [49, 55]. Improvement in the graft dysfunction rate in recent times can be attributed to better medical management of mild PGD with the use of levosimendan, nitric oxide, and phosphodiesterase inhibitors. The short-term survival for ACHDR is poorer as compared to NCR, and primary graft dysfunction remains a significant issue affecting short-term survival in ACHDR. The fact that the ACHDR who survives the first post-transplant year have better long-term survival than NCR indicates that perioperative mortality and morbidity is most likely the Achilles heel for cardiac transplantation in ACHDR [54]. Management of severe PGD with early intervention and short-term mechanical support appears to have improved survival [5].

3. Mechanical circulatory support

MCS may be provided by VA-ECMO or the implantation of a temporary paracorporeal ventricular assistance device (VAD) and the choice depends on the knowledge about devices and shelf-available items. There’s no manual or evidence-based decision-making protocol to choose one or another. Nevertheless, ECLS management may determinate success to discharge of patients experiencing PGD.

Advances in durable MCSs (LVADs) made its use reliable in patients with heart failure as a bridge to heart transplant, as well as postoperative support with ECLS in PGD HT to allow organ recovery. Although an LVAD is usually the choice for consistent outcomes in patients supported while waiting for a heart transplant, ECLS may be used in patients in whom LVADs, BiVADs, or TAH (total artificial hearts) are not reliable or available. It includes patients who are likely to receive a heart transplant within a short time period after listing.

ECLS use in heart transplant PGD continues to be the first line of support with some recent evidence of improved outcomes. There is some evidence on the use of short-term VAD but with limited results in a real-world setting [61]. Although further studies are necessary to understand the optimal role of ECLS in heart transplantation the objective of this chapter is to discuss its role in PGD, that accounts for 40–50% early mortality after heart transplantation according to studies using the International Society of Heart and Lung Transplantation (ISHLT) registry [5]. Mechanical circulatory support may be provided by VA-ECMO or implantation of a temporary VAD. 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 [62].
The 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 from PGD. In this study, the authors found no difference in weaning when comparing peripheral ECMO and central ECMO (50%) but a higher rate of vascular complications (18%) in patients supported on peripheral ECMO.

The device of choice and timing of insertion varies among institutions, and the use of mechanical circulatory support tends to be more liberal for early support in high-volume centers with a potentially positive effect on graft recovery [63]. Although ECMO has been traditionally favored due to the ease installation, and the ability to provide oxygenation following a prolonged cardiopulmonary bypass, its use is associated with increased risk of bleeding, insufficient LV unloading, and the chance of intracardiac thrombosis in patients with minimal systolic function [64, 65].

Takeda and colleagues from Columbia University performed an analysis of patients requiring mechanical support for PGD following heart transplant [66]. Of the 597 patients who received a heart transplant during the study period, severe PGD developed in 44 (7.4%). Within 24 h 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. A total of 10 patients (59%) were weaned from VAD support, and 24 patients (89%) were removed from VA-ECMO support after adequate graft function recovery. The 3-year post-transplant 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 reasons. Tran and colleagues [67], from UCLA, demonstrated that patients requiring ECMO for graft failure after heart transplant had lower mortality (51.6%) when compared with patients who needed ECMO for other etiologies (69.1%).

ECLS/ECMO seems to be the best way to support PGD patients in almost all scenarios for many reasons. It can provide safe maximum flow and pulmonary support with different cannulation strategies—percutaneously, hybrid, or by central access. It is rapidly installed, and cost of disposable equipment is relatively inexpensive compared with other devices. In basic settings, veno-arterial (VA) ECMO is considered the main strategy. Central access is preferable due to fast installation, direct evaluation of the heart decompression, and easiest way to install a left-side drainage cannula in the left atrium or left ventricle if it remains distended.

A total of 16% of our PGD patients had a left cannula installed as a venting strategy to guarantee LV resting. Our preference is to use central VA ECMO. Patients may be extubated as any other heart surgery postoperatively after recovering from anesthesia. Cannulas may be positioned inferiorly through the thoracic wall and the chest fully closed to facilitate mobility and ambulation. Extubation may be done even if only the skin is closed—not sutured sternum. In this case, the care team has to ensure a sealed bandage around the cannulas to avoid pneumothorax formation.
Full support is sufficient when hemodynamic variables and microperfusion are normalized—VA ECMO usually provides normal oxymetric parameters if the patient is well supported. MAP goal usually is around 70, CVP < 15, SVO\textsubscript{2} > 60\%, serum lactate < 2.0 mmol/L, and \textsubscript{O}2 saturation > 95\%. Since the pulmonary flow is shunted through the ECLS system, pulmonary artery pressures are expected to be very low, and most of the times cardiac index cannot be measured. Pulsatile waveforms are almost invisible or show a very low pulse pressure gradient (less than 20 mm Hg).

Usually, in the range of 3–7 days, it is possible to see some degree of heart recovery. Pulse pressure may rise above 20 mmHg, CI may be measurable through PAC, pulmonary pressures may rise, and the patient may be hemodynamically stable with a lower flow on ECLS system. At this point, the weaning protocol should require an echocardiographic evaluation to reassess biventricular function. In adults, patients showing aortic time-velocity integral (VTI) ≥ 10 cm, left ventricular ejection fraction (LVEF) > 20–25\%, and lateral mitral annulus peak systolic velocity (TDSa) ≥ 6 cm/s at minimal ECMO flow were all successfully weaned [68].

Although ECMO may provide adequate support, it has limitations such as insufficient LV unloading, limited time of support, and risks of thromboembolic and vascular complications. High pressures in left chambers may not be easily documented, and the patient may run with hemodynamic instability. Non-treatable low flow related to sequestration of stroke volume in the lungs, secondary of left chambers distention, and inability of the heart to decompress from ECMO post-load augmentation may be seen. A documented left-side heart high pressure requires an immediately strategy to unload left chambers and re-establish the desired flow. A drainage cannula in left atrium or ventricle that allows a fast connection on the ECMO circuit permits good drainage and is a feasible choice. It is important to note that, in this case, optimum flow will be achieved after a left-side drainage cannula insertion.

In case of recovery of the left ventricle’s ability to unload, the left cannula may be removed before starting the weaning protocol or just reducing the ECMO to allow filling up the ventricle and considering weaning. Intra-aortic balloon pump has been documented, but in a different scenario setting, as a way to reducing systemic vascular resistance, helping to prevent LV distention, during the VA ECMO run [69]. More recently, in the largest US-based retrospective study, the addition of Impella to VA-ECMO for patients with refractory cardiogenic shock was associated with lower all-cause 30-day mortality, lower inotrope use, and comparable safety profiles as compared with VA-ECMO alone. This study reinforces the importance of LV decompression as an important factor to improve outcomes during VA ECMO in severe ventricular dysfunction [70].

If recovery is not noted on PGD, other strategies should be considered and palliative care may be an option. Although we were able to prolong ECMO support in an infant up to 44 days until recovery, a biventricular support including a durable VAD or a total artificial heart may be an option in selected patients. Since there is lack of evidence to support use of those alternatives on PGD, the selection of a device should be made according to the patient’s clinical condition and the center’s experience.

3.1. Personal experience

Between January 2007 and December 2013, a total of 71 heart transplantations were performed in patients with advanced heart failure and 11 (15.5\%) of these patients presented PGD [71].
All patients had advanced heart failure and 2 (18.2%) patients were in a priority state before the transplantation. As for the etiology of the cardiomyopathy, 5 (45.4%) were due to Chagas disease, 3 idiopathic dilated cardiomyopathy, 1 from secondary to valvular cardiomyopathy, 1 had restrictive cardiomyopathy, and 1 was associated with peripartum cardiomyopathy. None of the patients had PRAC—preformed antibodies calculated panel—above 10%.

In our experience, the causes of PGD were not associated with severe rejection, as documented by routine endomyocardial biopsy in the first week, with only one patient presenting cellular rejection greater than 2R. Donors were predominantly male (n = 7; 63.6%) and had an average age of 26.6 ± 12.3 years (ranging from 15 to 48 years). The causes of death among donors included head trauma in 7 cases (63.6%), hemorrhagic stroke in 3 (27.3%), and cerebral tumor in 1. A total of 7 cases (63.6%) received continuous infusion of norepinephrine >0.1 mcg/kg/min at the time of the retrieval. Retrievals took place in the same hospital of the implantation in 6 (54.5%) cases and at a distant center in the 5 remaining cases. The average ischemia time was 151 ± 82 min (ranging from 73 to 270 min), with 82.8 ± 14.2 min in the local retrievals and 233 ± 35.4 min in distant retrievals (p < 0.0001). The cold ischemia “limit” of 4 h was exceeded in 2 (18.2%) patients.

In this group of patients, the use of ECMO met the desired goals, promoting cardiac recovery in most cases, with acceptable complication rates, considering the severity of the clinical condition of patients [71]. We were successful in removing the ECMO, with cardiac recovery in 81.8% of the patients after an average of 76 h. The main postoperative problems that we found were acute renal failure, stroke, and requirement for surgical revision of hemostasis. The first is a frequent complication [72] and is secondary to multiple insulting factors—shock, nephrotoxic drugs, and systemic venous congestion—and pre-transplant cardiorenal syndrome. Renal function recovered in all patients after a few sessions of hemodialysis, as described by Listijono et al. [73]. The last two are complications related to the requirement of anticoagulation during ECMO, which is difficult to control. Complicating factors are recent heart surgery, the presence of shock with concomitant hepatic dysfunction, and, eventually, disseminated intravascular coagulation. Excessive use of blood products complicates immunological sensitization, systemic congestion—including liver congestion, which increases bleeding—and pulmonary hypertension. The use of heparin-coated circuits, antifibrinolytics, careful surgical technique, maintenance of hemodynamic stability with systemic venous decompression, and synthetic derivatives of coagulation factors are important to minimize these complications. Although patients who developed stroke showed increased hospital mortality, those who survived had full recovery of motor activity without limitation in their quality of life.

4. Conclusion(s)

The aim of circulatory assistance in PGD is always cardiac recovery. Thus, the characteristics of the ideal device must comply with the following requirements: ability to be quickly installed, allowing the rapid re-establishment of cardiac output in order to maintain adequate tissue perfusion and reverse multiorgan dysfunction, reducing ventricular filling pressures, promoting myocardial protection with increased coronary flow, and having a low complication rate.
Heart decompression is important for a successful recovery since intracavitary hypertension curtails subendocardial coronary perfusion, especially in those patients who had no electrical activity or lacked sufficient contractile activity for adequate LV decompression.

Regardless of showing complete recovery, patients with PGD have a higher mortality when multiple organs were involved. Hence, there is need for strengthened intensive care in this population, systematically focused on the management of organs and systems and on the prevention of sepsis.

The rapid hemodynamic deterioration due to PGD shows that the earlier the implantation (operation room), the best are the outcomes for weaning and survival. Patients in whom ECMO was initiated due to cardiac arrest had a poor outcome, and the appropriate timing was certainly neglected.

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Conflict of interest

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