Primary graft dysfunction in heart transplantation: How to recognize it, when to institute extracorporeal membrane oxygenation, and outcomes

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Feature Editor's Introduction—*Primary graft dysfunction (PGD) after orthotopic heart transplantation is the most common condition associated with mortality in the early postoperative period. Citing recent retrospective studies on the subject, Dr Hull and colleagues make the point that PGD is common, occurring in up to 30% of patients, with an associated 50% mortality if mechanical circulatory support (MCS) is required, which is the case in approximately one-half of cases. Recognizing that an understanding of the donor and recipient characteristics that increase the likelihood of PGD is the sine qua non for minimizing its occurrence, the authors have created a table that can easily serve as a "checklist" to use at the time of the donor offer to aid decision making. Furthermore, they emphasize the importance of grading PGD based on the 2014 International Society for Heart and Lung Transplantation consensus statement using the classifications mild, moderate, and severe. Differentiating mild from severe PGD is quite straightforward, but incorrectly assessing PGD as moderate (ie, able to be managed pharmacologically) as opposed to severe may delay more aggressive therapy and compromise outcomes. Among the several messages that the reader can glean from this article are (1) the importance of recognizing the onset of severe PGD, which mandates the immediate institution of MCS; (2) improved outcomes are associated with the early use of venoarterial extracorporeal membrane oxygenation (VA-ECMO), as opposed to temporary univentricular support; and (3) a delay in instituting MCS of even several hours significantly diminishes survival. The authors present interesting data suggesting that heart transplantation resulting from donation after cardiac death may in fact yield results comparable to donation after brain death, as long as there is liberal use of VA-ECMO in those experiencing PGD.*

The authors address virtually all of the basic clinical questions that arise in the management of PGD. Furthermore, and to our benefit, they provide a well-organized, well-referenced, and superbly written framework for postoperative care of these patients.

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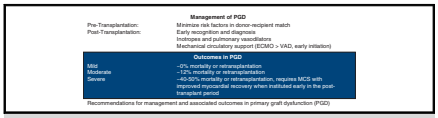

Recommendations for management and associated outcomes in primary graft dysfunction.

CENTRAL MESSAGE

Primary graft dysfunction (PGD) is the most common cause of mortality early after heart transplantation. Early implementation of venoarterial extracorporeal membrane oxygenation improves survival in severe PGD.

See Commentary on page 134.

Primary graft dysfunction (PGD) is the leading cause of mortality early after cardiac transplantation.[1] Broadly, PGD is defined as single or biventricular allograft dysfunction that leads to hypotension from a reduced cardiac output that is insufficient to meet the circulatory demands of the recipient and occurs <24 hours post-transplantation. In 2014, the International Society for Heart and Lung Transplantation (ISHLT) published guidelines from a consensus conference that codified the definition, diagnosis, and management of PGD. These guidelines were based on input from 71 experts from 42 heart transplant centers worldwide.[2]

Before the guidelines were established, each transplant centers used its own set of criteria to define PGD. These criteria varied by institution and often included such

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variables such as echocardiographic data, time after surgery, and need for mechanical circulatory (MCS) or inotropic support. The RADIAL score, based on right atrial pressure >10 mm Hg, recipient age >60 years, diabetes, inotrope dependence, donor age >30 years, and duration of ischemia >4 hours, was the only validated system available for predicting PGD.[3] A higher RADIAL score corresponds to an increased incidence of PGD[4] and in-hospital death among PGD patients.[5] In this Expert Opinion, we focus on data generated after publication of the consensus guidelines, which were essential to (1) standardize the definition of PGD across transplant centers, (2) allow for a systemized comparison of independent reports on PGD risk factors, management, and outcomes among centers; and (3) promote the forward momentum of interventions for PGD and its scientific study.

PGD DEFINITION, INCIDENCE, AND RISK FACTORS

The ISHLT consensus guidelines distinguish between PGD and secondary graft dysfunction, with the latter being attributed to a discernible cause such as hyperacute rejection, pulmonary hypertension, a surgical complication or a systemic issue, such as sepsis. PGD is further classified as left ventricular (L-PGD) or right ventricular (R-PGD). L-PGD includes biventricular dysfunction and is graded as mild, moderate, or severe based on the extent of inotropic or mechanical support needed to maintain cardiac function (Table 1).[2] With a standardized definition of PGD established, the diagnosis of this disease phenomenon and an understanding of its risk factors (Table 2) and incidence are possible (Table 3; Figure 1).

Importantly, the ISHLT guidelines have been independently verified in subsequent studies, 3 of which we discuss briefly herein. In 2017, Sabatino and colleagues[5] reported that in 518 patients who underwent heart transplantation between 1999 and 2013, 72 (13.9%) met the ISHLT criteria for PGD (5% mild, 46% moderate, 49% severe). The majority (78%) experienced biventricular L-PGD, which was associated with a significantly worse prognosis compared with isolated ventricular involvement. Unsurprisingly, the occurrence of PGD was associated with a significantly higher risk of death or the need for retransplantation compared with normal graft function (27% vs 3%; $P < .01$), which occurred at an incidence of 65% in severe PGD, 12% in moderate PGD, and 0% in mild PGD.[5] Mortality alone was 54% in severe PGD. Of the 35 patients with severe PGD treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO) (mean duration, 6 days), 11 (31%) died, 4 underwent retransplantation, and 20 (57%) were eventually weaned from support, although 8 patients subsequently died.[5]

In a second study reported by Foroutan and colleagues in 2018,[8] the incidence of L-PGD in 412 heart transplant

TABLE 1. Definitions of PGD: type and grade

Types of early graft dysfunction (diagnosis made with imaging and hemodynamic data, not pathologic information)		
PGD: Incidence 3%-30% Occurs within the first 24 h of surgery and is not due to a discernible secondary cause	SGD: Results from a discernible cause of graft dysfunction: - Hyperacute rejection - Pulmonary hypertension - Surgical complication - Sepsis	
Types of PGD L-PGD: includes left ventricular and biventricular dysfunction R-PGD: isolated right ventricular dysfunction, diagnosed based on the following: - Need for RVAD, or - RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2 L/min/m^2 and TPG < 15 mm Hg or PA systolic pressure < 50 mm Hg		
Grade of L-PGD based on severity		
Mild LVEF ≤ 40% or >1 h of CI < 2 L/min/m^2, RAP > 15 mm Hg, and PCWP > 20 mm Hg, on low-dose inotropes	Moderate Mild + MAP < 70 mm Hg for >1 h and high-dose inotropes or requirement for IABP	Severe Need for MCS other than IABP: - VA-ECMO - LVAD or biVAD

Early graft dysfunction can be classified as either PGD or SGD. In 2014, PGD was further defined by ventricular involvement and severity by the International Society for Heart and Lung Transplantation, from which this table is adapted.[2] *PGD*, Primary graft dysfunction; *SGD*, secondary graft dysfunction; *L-PGD*, left ventricular primary graft dysfunction; *R-PGD*, right ventricular primary graft dysfunction; *RVAD*, right ventricular assist device; *RAP*, right atrial pressure; *PCWP*, pulmonary capillary wedge pressure; *CI*, cardiac index; *TPG*, transpulmonary gradient; *PA*, pulmonary artery; *LVEF*, left ventricular ejection fraction; *MAP*, mean arterial pressure; *IABP*, intra-aortic balloon pump; *MCS*, mechanical circulatory support; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *LVAD*, left ventricular assist device; *biVAD*, biventricular assist device.

TABLE 2. Risk factors for PGD

Recipient	Donor	Perioperative and procedural
- Age and weight	- Older age	- Graft preservation strategy
- Comorbidities	- Cause of death (trauma)	- Ischemic time
- MCS or mechanical ventilation	- Duration of downtime	- Sex mismatch
- Reoperation, retransplantation, or multiorgan transplant	- Decreased cardiac function, valvular disease, LVH, or CAD	- Size mismatch
	- Requirement for inotropic or hemodynamic support	- Transfusion requirement
- Pulmonary vascular resistance*	- Comorbidities or sepsis	- Emergent transplant
- Sensitized or infected recipient	- Drug abuse	- Transplant team experience
- Congenital heart disease	- Laboratory tests: hormones, troponins, sodium	

MCS, Mechanical circulatory support; *LVH*, left ventricular hypertrophy; *CAD*, coronary artery disease. *Pulmonary hypertension is a cause of secondary graft dysfunction, but even within accepted ranges of pulmonary artery pressures for heart transplantation, lower pulmonary resistance is associated with decreased risk of PGD

recipients as defined by the ISHLT guidelines was 17% (3.6% mild, 9.5% moderate, and 3.9% severe) and there was a significant association between 1-year mortality and moderate and severe L-PGD, with a 30-day mortality of 52.6% in severe PGD. In a third study, Nicoara and colleagues[7] reported a 31% incidence in PGD (99 of 312 patients), along with significantly higher 30-day mortality in patients with PGD compared with patients with normal early graft function (6.06% vs 0.92%; $P = .01$). Collectively, these reports demonstrate that approximately 3% to 30% of heart transplant recipients experience some degree of PGD, and that patients with more severe PGD experience worse outcomes.

Preoperative donor and recipient risk factors can be used to predict the occurrence of PGD and avoid high-risk donor–recipient combinations that portend predictably unfavorable survival (Table 2). Specific factors more commonly associated with nonrecovery from severe PGD include combinations of advanced donor and recipient age, ischemia time, pretransplant recipient diabetes, and hemodialysis.[5] Another study identified donor ischemia time, African American race, and higher pretransplantation right atrial pressure as key risk factors for the development of PGD.[7]

Although distinguishing PGD, subclinical ischemia-reperfusion injury (IRI), and acute rejection is of clinical importance given the significantly different treatment strategies, there is a striking paucity of information on the cellular and molecular mechanisms of PGD in heart transplantation. Owing to the nature of the operation, IRI is a consequence of all transplantations, although its extent and severity can be modified by such factors as donor circumstances, ischemic time, and procurement conditions—factors that also affect the development and severity of PGD (Table 2). Although all cardiac allografts are subjected to IRI, not all develop PGD. PGD is clearly multifactorial, although severe IRI is likely a principal cause.

TABLE 3. Management of PGD and expected outcomes

Management of PGD	
Pretransplantation	Minimize risk factors in donor–recipient match
Posttransplantation	Early recognition and diagnosis
	Inotropes and pulmonary vasodilators
	Mechanical circulatory support (VA-ECMO > VAD, early initiation)
Outcomes in PGD[5,6]	
Mild	0% mortality or retransplantation
Moderate	12% mortality or retransplantation
Severe	40%-50% mortality or retransplantation, necessitating MCS with improved myocardial recovery when instituted early in the posttransplantation period

A summary of considerations in preventing PGD based on informed selection of donor-recipient matches and managing PGD with associated mortality estimates for each grade as informed by an appraisal of the literature after publication of the 2014 International Society for Heart and Lung Transplantation Consensus Conference Guidelines.[2,5-7] *PGD*, Primary graft dysfunction; *VA-ECMO*, venoarterial extracorporeal membrane oxygenation; *VAD*, ventricular assist device; *MCS*, mechanical circulatory support.

PGD OUTCOMES AND TREATMENT

Treatment of PGD has been propelled rapidly in recent years by developments in MCS. Before the advent and wide implementation of MCS, severe PGD was associated with poor survival with medical management alone, including inotropes and medications to lower pulmonary vascular resistance (Table 3). However, these medications are commonly used in post–cardiac transplantation patients independent of the development of PGD and thus are not specifically PGD-targeted interventions. The purpose of MCS is to rest the cardiac allograft while myocyte recovery from IRI occurs while at the same time avoiding multisystem organ failure from a low-flow state. Options for MCS in PGD include temporary single and biventricular assist devices (VADs) as well as VA-ECMO, with the latter being used with increased frequency owing to superior outcomes and relative ease of institution, either at the conclusion of the transplant operation due to inability to wean from bypass or in a more emergent setting due to impending allograft failure early postoperatively.

A study published in 2017 demonstrated superior outcomes in severe PGD with the use of VA-ECMO compared

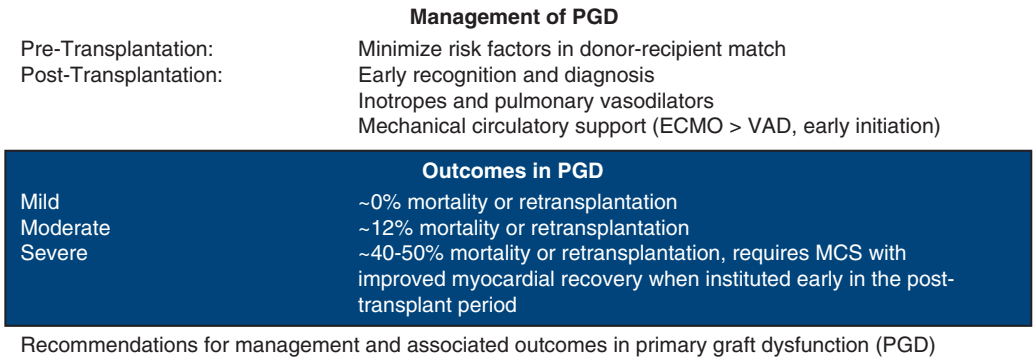

FIGURE 1. Recommendations for management and associated outcomes in primary graft dysfunction.

with VADs. Of 597 heart transplant recipients, 44 (7.4%) developed severe PGD necessitating MCS, including 17 who received an external VAD and 27 who were cannulated for VA-ECMO. Patients who received a VAD required longer cardiopulmonary bypass times and had significantly higher rates of major bleeding and renal failure. They also required longer support time (14 days vs 5.2 days on average; $P = .011$). In-hospital mortality was 27% overall and did not differ significantly between the 2 study arms ($P = .16$); however, the ability to wean from MCS due to eventual graft recovery was superior in the VA-ECMO group, in which support was more commonly initiated in the operating room (74%) via peripheral cannulation (85%) and left ventricular (LV) venting was not required (0%).[9]

Complications of VA-ECMO in PGD must be considered, including variable ventricular unloading without an LV vent, intracardiac stasis with the potential for clot formation, and vascular and thrombotic complications.[10,11] Cannulation strategies for PGD are not dissimilar from those used in general for postcardiotomy shock. A single optimal cannulation strategy and configuration mode that optimizes myocardial recovery and minimizes potential complications has not yet been agreed upon.[12] Configuration options include both peripheral and central cannulation, with no survival difference demonstrated between the two options in the postcardiotomy setting.[13] Central cannulation can be readily instituted using the cannulas placed for cardiopulmonary bypass, directing antegrade aortic flow. However, in our experience, bleeding from the aortic cannulation site can be an issue. Central VA-ECMO also may achieve more complete cardiac unloading, because the venous return cannula is directly in the right atrium. If an LV vent is needed in centrally cannulated patients, we preferentially use the right superior pulmonary vein (RVSP) or apex of the left ventricle, with the latter approach particularly useful when the left atrial suture line is close to the RVSP. Peripheral cannulation can be performed via an open (surgical cutdown) or percutaneous approach, with the former used more frequently and with fewer complications. Specific strategies including combinations between peripheral and central cannulation and the options for LV venting with VA-ECMO are beyond the scope of this Expert Opinion and are reviewed in detail in the 2020 postcardiotomy ECLS: Expert Consensus.[14]

The management of anticoagulation in patients on VA-ECMO in the post–heart transplantation setting is particularly important. Our preference is to place peripheral femoral cannulas in the right femoral artery and vein during full anticoagulation while on bypass. We then achieve full flow on VA-ECMO before administering protamine. The chest is closed, and a heparin drip is initiated 6 to 8 hours postoperatively when major coagulopathy has been corrected and chest tube output is <100 cc/hour. The heparin drip is then titrated to therapeutic levels (partial thromboplastin time 2.5 times normal) if the chest tube output remains at <100 cc/hour and hemoglobin is stable after 24 hours.

VA-ECMO lacks durability in patients who fail to experience myocardial recovery, and in these patients more durable options, such as a VAD or total artificial heart, may be required for salvage.[15] However, the duration of ECMO support in severe PGD generally ranges between 3 to 8 days, with longer duration of support predicting poor myocardial recovery and increased mortality.[16] Complications of ECMO support in immunosuppressed heart transplant recipients can be major causes of morbidity and mortality. They include infection, bleeding, stroke, and mediastinitis (in centrally cannulated patients), and are not entirely dissimilar from those seen in patients on ECMO for indications other than PGD.

Even before publication of the ISHLT guidelines, the role of ECMO in PGD was broadly recognized. A 2010 study reported by D'Alessandro and colleagues[17] showed superior survival with ECMO in 90 patients who developed graft dysfunction within 48 hours of transplantation. Survival was 46% (13 of 28) in patients who received maximal medical management, 25% (2 of 8) in those with a VAD, and 50% (27 of 54) in those treated with ECMO.[17] Although

in-hospital mortality was significantly higher in patients who developed early graft dysfunction, 1-year survival was not significantly worse in patients successfully weaned from VA-ECMO compared with those who did not develop early graft dysfunction. A follow-up study then demonstrated that recipient characteristics, including age >60 and preoperative MCS requirement, as well as donor characteristics including mean norepinephrine dose, trauma as the cause of death, LV ejection fraction <55%, and prolonged ischemic time, were predictors of severe PGD.[18] In that study, the rates of ECMO weaning and survival to discharge were 60% and 46%, respectively. Compared with patients without PGD, those with PGD had significantly worse survival at 1 year (78% vs 39%) and 5 years (71% vs 34%), but 1-year survival was not significantly worse in the patients who were successfully weaned from VA-ECMO.[18]

More contemporary studies that have used the ISHLT guidelines to diagnose PGD and grade its severity continue to support the use of VA-ECMO in severe PGD. A study of 1030 patients who received a heart transplant between 2005 and 2015 found that 31 (3%) developed severe PGD necessitating VA-ECMO.[6] Of these patients, 81% were weaned from VA-ECMO successfully, and 61% survived to discharge.[6]

The improved survival in patients with severe PGD managed with VA-ECMO raises the question of whether there is an optimal time posttransplantation to diagnose severe PGD and institute support. A recent study addressed this question in 38 (incidence of 10.5%) heart transplant recipients who developed severe PGD between 2005 and 2015. The patients were treated with prompt versus conservative institution of VA-ECMO, with a mean cannulation time of 1.95 hours versus 7.26 hours after transplantation, respectively. Patients in the prompt group experienced less in-hospital mortality (5% vs 28%; $P = .083$), despite no between-group difference in intensive care unit length of stay or the development of major complications. One-year survival trended toward improved in the prompt group (90% vs 67%; $P = .117$), as confirmed on multivariate analysis, which showed a 74.6% lower risk of mortality in the prompt group ($P = .094$). Overall, these findings suggest that early VA-ECMO initiation offers improved myocardial recovery in heart transplant recipients with severe PGD without increasing the risk of complications.[19] The utility of early institution of VA-ECMO was also demonstrated in earlier reports predating the ISHLT guidelines, showing excellent rates of weaning (87%) and survival to discharge (74%) in patients with severe PGD treated with early institution of VA-ECMO.[20,21]

Despite the significant progress made in understanding and treating PGD in recent years, many questions in the modern era of cardiac transplantation remain. Implementation of MCS is unnecessary in mild PGD but is clearly indicated in severe PGD. However, moderate PGD remains a gray area, and further investigation is needed to determine whether institution of MCS, particularly VA-ECMO, has a favorable risk–benefit profile in this important patient population. Additionally, the recent increase in the use of marginal-risk and high-risk donor hearts may drive overestimation of the incidence of PGD and thus a secondary increase in ECMO use. Determining the incidence of PGD with marginal donor cardiac allografts and how MCS can be most efficaciously implemented in the recipients of these allografts are important areas for future study. Interestingly, a study published in 2006 demonstrated that marginal allografts that were turned down for standard transplantation owing to coronary artery disease, LV dysfunction, or hypertrophy and a high inotropic requirement did not demonstrate an increased incidence of PGD, although overall mortality was significantly higher.[22]

Furthermore, as the use of donor after circulatory death (DCD) hearts increase, which results in a different set of noxious insults to the donor heart, largely due to increased periprocurement warm ischemic time but independent of the catecholamine surge in donor after brainstem death (DBD) hearts, the incidence of PGD and its management in DCD recipients will need to be carefully studied.[23] Currently, there is a paucity of data looking specifically at PGD in DCD versus DBD recipients, but in 2017 Messer and colleagues[24] reported no difference in 30-day or 90-day survival between DCD and DBD recipients, independent of the DCD procurement method (normothermic regional perfusion vs direct procurement and perfusion), including no difference in the need for MCS to support the recipients postoperatively. In a more recent study by Chew and colleagues,[25] 35% (8 of 23) of DCD recipients required VA-ECMO to wean off of cardiopulmonary bypass, and 7 were diagnosed with severe PGD. The average duration of VA-ECMO was 5 ± 2 days. All the recipients recovered to normal biventricular function at 1 week post-transplantation. These findings reinforce the importance of early VA-ECMO in PGD and suggest that comparable outcomes of PGD in DCD and DBD heart transplants.

In conclusion, despite numerous advances in heart transplantation in the modern era that have driven increased survival and better management of acute and chronic rejection, the incidence of PGD remains significant at 3% to 30%. PGD is the leading cause of early mortality after heart transplantation (Figure 1). As strategies to salvage marginal and high-risk donor organs and DCD transplantation become more common to address the organ shortage, the occurrence of PGD has increased over recent years.[5] Therefore, well-studied algorithms for the treatment of PGD are essential as the field advances. VA-ECMO, particularly with early implementation, is a mainstay of treatment of severe PGD. It improves survival in this patient population and

merits further attention to define specific cannulation strategies and configurations aimed at yielding an optimized risk–benefit profile in the context of prompt myocardial recovery and survival in patients with PGD.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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