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ISHLT CONSENSUS

Report from a consensus conference on primary graft dysfunction after cardiac transplantation

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Although primary graft dysfunction (PGD) is fairly common early after cardiac transplant, standardized schemes for diagnosis and treatment remain contentious. Most major cardiac transplant centers use different definitions and parameters of cardiac function. Thus, there is difficulty comparing published reports and no agreed protocol for management. A consensus conference was organized to better define, diagnose, and manage PGD. There were 71 participants (transplant cardiologists, surgeons, immunologists and pathologists), with vast clinical and published experience in PGD, representing 42 heart transplant centers worldwide. State-of-the-art PGD presentations occurred with subsequent breakout sessions planned in an attempt to reach consensus on various issues. Graft dysfunction will be classified into primary graft dysfunction (PGD) or secondary graft dysfunction where there is a discernible cause such as hyperacute rejection, pulmonary hypertension, or surgical complications. PGD must be diagnosed within 24 hours of completion of surgery. PGD is divided into PGD-left ventricle and PGD-right ventricle. PGD-left ventricle is categorized into mild, moderate, or severe grades depending on the level of cardiac function and the extent of inotrope and mechanical support required. Agreed risk factors for PGD include donor, recipient, and surgical procedural factors. Recommended management involves minimization of risk factors, gradual increase of inotropes, and use of mechanical circulatory support as needed. Retransplantation may be indicated if risk factors are minimal. With a standardized definition of PGD, there will be more consistent recognition of this phenomenon and treatment modalities will be more comparable. This should lead to better understanding of PGD and prevention/minimization of its adverse outcomes.

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At the 33rd Annual International Society of Heart and Lung Transplant (ISHLT) meeting, a consensus conference took place on April 23, 2013, to formulate guidelines to better define, diagnose, and manage the care of patients with primary graft dysfunction (PGD) in heart transplantation. The conference had 71 participants who had published in PGD or had vast clinical experience in heart transplantation, including cardiologists, cardiac surgeons, pathologists, and immunologists (Appendix A), who represented 42 heart transplant centers from North America, Australia, Europe, and Asia.

Before the conference, an online survey was used to obtain contemporary thoughts on diagnosis and management of PGD patients from transplant centers. Forty-seven transplant centers responded. Results of this survey are summarized in Table 1.

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Table 1 Primary Graft Dysfunction in Heart Transplantation, Results of Pre-conference Online Survey (47 centers participating) January 2013–March 2013

- Total number of transplant patients at all participating centers was 9,901 with 733 patients thought to have PGD—rate 7.4%
- 30-day mortality was 30% and 1-year mortality was 34.6%.
- Most common causes of death for 30-day mortality: Multiorgan failure (70%), graft failure (20%), and sepsis (10%)
- Definition parameters for PGD:
  - 79% of centers felt that LVEF $\leq$ 40% was a criteria of PGD
  - 68% of centers felt that a time frame of within 24 hours should be used to define PGD
  - 70% of participating centers felt that mechanical support is a mandatory criteria for the definition of PGD

Exclusion criteria for PGD: Hyperacute rejection, 85%;
- sepsis, 85%; right ventricular dysfunction with pulmonary artery systolic pressure >40%–59%; bleeding, 67%
- Precautions against PGD: descending order of importance
  - Cooling of the heart during implantation (by using devices such as cooling jackets, ice, cooling via vent into left atrium/ventricle)
  - Controlled reperfusion
  - Special cardioplegic solution protocol during surgery
  - Temperature control during transport
- Treatment
  - Retransplantation for PGD offered at 64% of participating transplant centers
  - Type of mechanical support routinely utilized (in order of most common to least common): Intra-aortic balloon pump, ECMO, VAD (paracorporeal), VAD (intracorporeal)

ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; PGD, primary graft dysfunction; VAD, ventricular assist device.

Although thought to be a fairly common entity early after cardiac transplant, many parameters regarding PGD are yet to be well defined. Most cardiac transplant centers use differing definitions when referring to PGD, making inter-center comparisons and research difficult to carry out. This underscores the fact that to further guide research and management in PGD, standardization of terminology is needed. A similar approach in lung transplantation led to a consensus definition in 2005 and to remarkable advances in the field during the following years.[1] The purpose of this conference was to initiate the process of standardization within the study of PGD. It was felt that the following topics were important to be addressed:

- Definition for PGD including the cardiac characteristics and time frame after transplant that lead to a diagnosis of PGD
- Specification of a grading system for severity of PGD
- Management of PGD according to severity
- Identification of donor risk factors for the development of PGD
- Development of a risk stratification tool that can be used before cardiac transplantation
- Identification of areas for further research

This report provides a summary of survey data collected before the conference, state-of-the-art presentations given at the consensus conference, and the conclusions of group sessions culminating in consensus statements for PGD. This report should serve as the current consensus within the cardiac transplant community regarding diagnosis, management, and risk stratification of post-transplant PGD and will allow for standardization in research and literature pertaining to PGD, thus permitting uniform comparisons between centers and studies to take place.

Clinical background

Although survival after cardiac transplantation has been improving for the last 2 decades, whether the incidence and mortality from PGD has followed suit is unclear from the literature.[2–4] This lack of clarity stems not from the amount of research conducted on the topic of PGD but instead from the lack of standardization of diagnostic criteria. Parameters such as requirement of inotropic support, left ventricular (LV) ejection fraction (LVEF), and requirement of cardiac mechanical support have all been put forth as possible criteria for PGD. Each transplant center uses a different set of criteria, making basic figures, such as incidence and mortality, difficult to compare over time as well as between centers.

An analysis of the United Network for Organ Sharing (UNOS) database was conducted for transplants occurring from 1999 to 2007 ($n = 16{,}716$). For this analysis, PGD was defined by "hard outcomes," meaning post-operative 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.[5]

Single-center data show that the incidence of PGD varies from 2.3% to 28.2%.[5–12] Such a wide range of incidence represents a wide range in definitions, encompassing differing parameters with respect to timing of onset, echocardiographic findings, hemodynamic measures, requirement of inotropic support, requirement of mechanical support, and exclusion of certain criteria such as rejection. Although ward length of stay was not significantly different for patients with PGD and those without, intensive care unit stay was longer for patients with PGD.[13]

Even with the dearth of standardization, much work has been done in the field to illuminate risk factors that lead to PGD and also to properly define treatments available. Because of the short time frame in which PGD is thought to develop and the numerous donor factors identified as potential risk factors, there are most likely donor physiology constituents that negatively affect cardiac function and continue after transplant.[3,5] Because decreased donor cardiac function and requirement of hemodynamic support are both risk factors for development of PGD, we can speculate that pathophysiologic dysfunction in the graft continues even after transplant. Another supporter of this argument is that donor biomarkers (as yet non-validated) have been found to be associated with development of PGD.[13,14]

From the risk factors that have been found for PGD, we can extrapolate that the preservation process of cardiac grafts also has a role in the development of PGD. With more than 100 heart preservation solutions available, certain solutions may possibly contribute to increased myocyte death and result in cardiac dysfunction. A recent retrospective study comparing 2 commonly used solutions (University of Wisconsin and Celsior) found that there was increased ischemia present in biopsy specimens for which Celsior solution had been used in the transplants. The severity of this ischemia was associated with the requirement of mechanical support and was also predictive of development of PGD.[15]

Although the literature on pathologic findings of PGD is scarce, we asked conference participants questions relating to autopsy findings for PGD patients in the pre-conference survey. The survey data show that most autopsies done on patients thought to have PGD will show signs of rejection, ischemia, edema, or reperfusion injury (Appendix B). Although this shows that the incidence of true PGD might be lower due to misdiagnosis, it does not, unfortunately, lead to further clues about the etiology of PGD. However, it must be remembered that PGD in clinical practice is a diagnosis made with the use of imaging and hemodynamic data, not with the aid of pathologic information.

State-of-the-art presentations

Epidemiology and outcomes: Josef Stehlik

Although ascertainment of the exact incidence of PGD from registry data is not possible, these data provide us with important information about the epidemiology and the clinical characteristics associated with PGD. Data of interest available in the ISHLT Transplant Registry (Registry) include donor, recipient, and transplant event characteristics, early mortality, and the causes of death.[2,4]

Examination of early mortality after heart transplant documented in the Registry reveals that 66% of the deaths that occur in the first 30 days after transplant are due to "graft failure" and "multi-organ dysfunction." Most of these events are probably the result of fatal PGD. A closer look at early mortality of more than 100,000 patients who received transplants between 1982 and 2011 shows that approximately 10% of patients die within 30 days of transplant, and this number increases to 14% by 90 days after transplant. Interestingly, the risk of early mortality varies by etiology of heart disease leading to the need for transplant. The risk of 30-day and 90-day mortality is highest for retransplant (18% and 22%) and congenital heart disease (17% and 21%), intermediate in valvular cardiomyopathy (14% and 18%), and lowest in ischemic (10% and 14%) and non-ischemic (8% and 12%) cardiomyopathy patients. 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.

The era of transplantation is an important factor as well. Continued gradual improvement of survival after transplant during the past 3 decades has been well documented and attributed mostly to lower mortality in the first year after transplant. This improved survival is realized very early after transplant, with 30-day and 90-day mortality of 12% and 17% in patients who received a transplant in 1982 to 1992, 10% and 14% for those in 1993 to 2002, and 8% and 11% for those in 2003 to June 2010. It should be noted, however, that whereas improvement in survival took place in patients of different heart disease etiologies, the degree of this era effect varied among these groups. Focusing only on the 24,021 adult patients who received a transplant between 2003 and June 2010, we see that early post-transplant survival in patients of all the different heart disease etiologies is better than in the previous eras; however, differences among groups still exist. The 30-day and 90-day mortality is 15% and 18% for congenital heart disease, 12% and 17% for valvular cardiomyopathy, 10% and 14% for retransplant, 8% and 11% for ischemic, and 7% and 10% for non-ischemic cardiomyopathy patients.

In summary, Registry data indicate that a sizable majority of early post-transplant deaths likely result 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.

Pathogenesis of PGD: Peter Macdonald

The donor heart is subject to a series of insults during the transplant process—brain death and its sequelae in the donor, hypothermic ischemia during transport, warm ischemia during implant surgery, and finally, reperfusion injury after release of the aortic cross-clamp in the recipient. In addition, systemic factors in the recipient may create a "hostile" environment that further compromises donor heart function after reperfusion. Hence, donor, procedural, and recipient factors may all contribute to the development of PGD.

Brain death in the donor is associated with a series of events that result in impaired myocardial contractility and sensitize the heart to ischemia–reperfusion injury. These events include the intense release of myocardial norepinephrine immediately after brain death that results in mitochondrial and cytosolic calcium overload.[16] Depending on its extent, mitochondrial calcium overload may activate autophagy, apoptosis, or necrosis.[17] Calcium overload of the contractile proteins leads to contracture and is associated with a characteristic histologic appearance known as "contraction band necrosis."[18–20] Administration of exogenous catecholamines during donor resuscitation may contribute to desensitization of myocardial β-receptor signaling after brain death and to activation of multiple

pro-inflammatory mediators, including complement.[21–23] In addition, decreased serum levels of various hormones, including triiodothyronine, cortisol (after a transient increase), and insulin have been reported and likely contribute to the depression of myocardial contractility.[24]

Donor hearts vary markedly in their ability to tolerate the period of cold and warm ischemia that is obligatory in all heart transplant procedures. Hearts from older donors are particularly susceptible to ischemic injury.[25] This may be partly due to unrecognized coronary artery disease or pathologic LV hypertrophy in donors with a history of hypertension.[26] In addition and perhaps more important, there is an age-related decline in endogenous cardioprotective mechanisms such as ischemic pre-conditioning and post-conditioning.[27] Restoration of these endogenous cardioprotective mechanisms by pharmacologic agents that directly activate the intracellular signaling pathways or their targets is an attractive approach to mitigating the effect of ischemia in aged donor hearts.

Most donor hearts are stored in a cold preservation solution and transported on ice. Hypothermic storage slows but does not completely arrest cellular metabolism. Consequently, progressive ischemic injury is an inevitable consequence of prolonged static storage. In addition, loss of normal aerobic metabolism paralyzes the transmembrane Na^+/K^+ adenosinetriphosphatase pump, leading to cellular swelling, and the switch to anaerobic metabolism during cold storage results in a rapid decline in high-energy phosphates and the development of lactic acidosis.[28] Intracellular acidosis activates the Na^+/H^+ exchanger, which exchanges H^+ for Na^+ across the cell membrane.[29] Rising intracellular Na^+ in turn drives the Na^+/Ca^+ exchanger, with the net result being an accumulation of intracellular Ca^{2+}.

Reperfusion of oxygenated blood to the heart 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.[30] The combination of Ca^{2+} overload and high oxidant stress in an energy-depleted cardiac myocyte activates formation of the mitochondrial permeability transition pore (MPTP), a non-specific channel that forms in the mitochondrial membrane and allows pro-apoptotic factors, such as cytochrome C, to be released into the cell cytoplasm.[31] Water entering by the MPTP causes mitochondrial swelling and may lead to membrane rupture, triggering necrotic cell death. Drugs that inhibit MPTP formation, such as cyclosporine, have been shown to reduce reperfusion injury and provide another potential therapy to mitigate ischemia–reperfusion injury in the setting of heart transplantation.[31,32]

Recipient factors may also contribute to early graft dysfunction. There are 2 clinical scenarios where this is likely to occur. The first is the presence of a high pulmonary vascular resistance in the recipient.[33–35] In this circumstance, 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.[11]

The second scenario is when there is activation of the systemic inflammatory response in the recipient resulting in a vasodilated systemic circulation that is refractory to conventional vasopressor support.[36] Risk factors for this "vasoplegic" response include mechanical circulatory support before transplantation, prolonged cross-clamp time, and large transfusion requirements.[37] In this circumstance, the "hostile environment" of the recipient results in PGD. The pathophysiology of PGD in this setting is poorly understood but 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.[36,38]

Risk factors for PGD: Javier Segovia

Several publications on this field have identified a variety of factors associated with the development of PGD. The high variability of results is attributed to diverse definitions of PGD, different eras of heart transplantation, different sources of information, with some reports analyzing large multicenter databases with limited number of variables relating to PGD and others derived from retrospectively reviewed single series, and different baseline characteristics of heart transplant patients, such as adult vs pediatric, emergency vs elective heart transplant.

However, all of the articles published have some common points. The multiple risk factors for PGD include not only donor and perioperative factors but also recipient characteristics, confirming the multifaceted nature of PGD. In fact, recipient risk factors may be more influential than donor or procedural variables, as shown in many published reports. The most consistently identified risk factors for PGD arising from the literature include recipient factors such as age,[11] parameters reflecting pulmonary hypertension (even within accepted limits for heart transplant), and more severe pre-transplant condition, including dependence on intravenous inotropic support, mechanical support, and mechanical ventilation.[5,39–41] Donor factors include age,[5,11,39] female donor[41] (to male recipient in some series), and cause of brain death.[3] Procedural factors include ischemic time[5,9,42] and donor-to-recipient weight mismatch (Table 2).[5,40]

The only validated scoring system for the prediction of PGD is the RADIAL score.[11] 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 (risk ratio ~2) were identified to form the acronym RADIAL: 4 are related to the recipient: Right atrial pressure > 10 mm Hg, Age > 60 years, Diabetes and Inotropic support dependence; and 2 are related to the donor: Age > 30 years and Length of ischemia time > 240 minutes. The presence of each of these factors in an individual patient adds 1 point to the final score. The risk of PGD was closely related to the RADIAL score in the

Table 2 Risk Factors for Development of Primary Graft Dysfunction

Donor risk factors	Recipient risk factors	Surgical procedural risk factors
Age[5,11,39,66]	Age[11]	Ischemia time[5,9,42]
Cause of death[40,68]	Weight[42]	Donor-recipient sex mismatch[41]
Trauma[8,11]	Mechanical support[5,39–41]	Weight mismatch[5,40]
Cardiac dysfunction[40,69]	Congenital heart disease as etiology of heart failure[5]	Non-cardiac organ donation[a,10]
Inotropic support[8,40]	Multiple reoperations	Experience of procurement team and center volume[5]
Comorbidities: diabetes, hypertension[2]	LVAD explant	Cardioplegic solution[15]
Downtime of cardiac arrest	Comorbidities: renal dysfunction, liver dysfunction (high MELD), DM	Increased blood transfusion requirement
Drug abuse: alcohol, cocaine, amphetamines	Ventilator dependent	Elective vs emergency transplant[b,70]
Left ventricular hypertrophy	Multiorgan transplant	
Valvular disease	Elevated PVR	
Hormone treatment	Allosensitization	
CAD/wall motion abnormalities on TTE	Infection	
Sepsis	Retransplant	
Alternate list/marginal donor allocation—not increased risk[7]		
Troponin trend		
Hypernatremia		

CAD, coronary artery disease; DM, diabetes mellitus; LVAD, left ventricular assist device; MELD, Model for End-stage Liver Disease; PGD, primary graft dysfunction; PVR, peripheral vascular resistance; TTE, transthoracic echocardiogram; UNOS, United Network for Organ Sharing.

[a]Donation of all noncardiac organs, with the exception of lung donation, was associated with decreased incidence of PGD using data from UNOS.[5] Alternative study shows a high degree of correlation between heart and lung PGD in patients undergoing a paired transplant

[b]Single-center study showed an incidence of 36% of PGD in the group that received an emergency heart transplant whereas the incidence was 16% in those for which the transplant was done electively.

derivation cohort, with a C-statistic of 0.74 in the receiver operating characteristic curve.

In a second experience, the same authors analyzed PGD incidence and validated the RADIAL score in an external, contemporary cohort of 698 heart transplants performed in 15 heart transplant programs in Spain from 2006 to 2010.[43] The overall incidence of moderate and severe cases of PGD was 22%. Isolated right ventricular (RV) failure was documented in 45% of the patients, and LV dysfunction was present in the remaining 55%, usually as a part of biventricular failure. A mechanical assist device was used for therapy in 50% of patients, and 30-day mortality of patients with PGD was 40%. One of the most important findings was that overall PGD-related mortality (58% in this series) is not confined to the first 30 days, as previously thought. It extends through the first 3 months after heart transplant and is frequently attributed to other causes such as multiorgan failure and sepsis.

The authors validated the RADIAL model in this cohort, by defining 3 groups with low (0–1 points), medium (2 points), and high ($\geq$3 points) risk for PGD. The incidence of PGD in each group was 12%, 19% and 28%, respectively ($p < 0.001$). The odds ratios for the incidence of PGD in the intermediate-risk and high-risk groups compared with the low-risk group were 1.75 and 2.76, respectively. Two limitations must be noted before applying this model in clinical practice. The RADIAL score in the validation cohorts showed good stratification ability (relative risks of PGD were clearly increased in higher risk groups), but there was poor calibration (exact prediction of absolute PGD incidence). Therefore, it must be used as a way to classify the PGD risk and not as an accurate predictor of PGD incidence in an individual patient. In addition, this score was derived and validated in populations of recipients with a low prevalence of ventricular assist devices (VADs), a group that is rapidly increasing in the current era. New analyses of PGD risk factors in large, contemporary series that include high proportions of recipients bridged with VADs are advisable.

Biomarkers of PGD: Andreas Zuckermann

The role of biomarkers in PGD remains controversial. Several biomarkers are commonly upregulated in brain death and there is debate about whether they should be used to define whether a heart is acceptable or non-acceptable and whether they can predict long-term outcomes in recipients with regard to PGD. In the literature, 22 prospective observational studies have addressed the role of 7 different biomarkers in predicting dysfunction in donor hearts or outcomes in recipient patients. This section summarizes and evaluates the research and status of possible biomarkers.

Traditionally used for diagnosis of myocardial infarction, elevated troponins in potential donors have been correlated in some studies with LV dysfunction, pulmonary edema, need for drug support, and worse outcomes in transplant recipients. Some studies have demonstrated that cardiac troponin I (cTnI), the alternative isoform of troponin, is reduced by donor treatment. Deibert et al[44] assessed the clinical significance of elevated cTnI levels in patients with non-traumatic subarachnoid hemorrhage and found that an elevated cTnI ($\geq$1.4 μg/liter) was a strong indicator of LV dysfunction in patients with subarachnoid hemorrhage.

However, the cardiac dysfunction was reversible and should not necessarily preclude these patients from undergoing operative interventions or becoming heart donors. Bocchechiampe et al[45] assessed not only 187 potential heart donors but also early outcomes in recipients, in relation to cTnI. They found that in potential heart donors, cTnI was associated with myocardial dysfunction (measured by LVEF and segmental wall motion abnormalities) and non-acceptance of the heart for transplantation, although whether this was reversible was not mentioned.[45] However, cTnI values in heart donors did not appear to be associated with PGD or recipient survival after transplantation.

Khush et al[46] conducted a further retrospective study assessing potential donor hearts and outcomes in recipients. Of 139 transplants, 43 had elevated cTnI. Although there was a non-significant trend towards longer post-transplant hospitalization in recipients of grafts from donors with elevated cTnI levels (17 days vs 15 days, $p = 0.044$), no association was found between elevated troponin (> 1.0 μg/liter) and the recipient's need for mechanical circulatory support, or 30-day and 1-year mortality between the 2 groups.[46] This demonstrated that an elevated troponin was therefore not a contraindication to transplant. Potapov et al,[47] however, did find that a cTnI value > 1.6 μg/liter in donors as a predictor of early graft failure had a specificity of 94%, and a cardiac troponin T (cTnT) value of > 0.1 μg/liter had a specificity of 99%; patients had poorer cardiac function and further need for inotropic support.

In summary, the status of troponins as a predictor for PGD remains controversial, because the literature demonstrates overall mixed results. Although a predictor for donor heart dysfunction, this systolic dysfunction is reversible, and there is no evidence to rely on troponin as a marker for PGD.

Tumor necrosis factor-α (TNF-α) is a cytokine synthesized by myocardial cells in response to stress (myocardial infarction, increased left ventricular pressure, volume overload). Animal studies have demonstrated TNF-α is upregulated in the heart after brain death.[48] Birks et al[49] used reverse transcriptase polymerase chain reaction to study the expression of TNF-α in donor myocardium and its relationship to early RV failure after transplantation. They found that TNF-α had a sensitivity of 87.5% and specificity of 83.3% as a predictor for RV failure in recipients. In addition, higher TNF-α messenger RNA (mRNA) was found in myocardium of unused donor hearts, and unused donor hearts had significantly higher serum TNF-α. This has raised the possibility of TNF-α as a biomarker for PGD.

Interleukin-6 (IL-6) is another cytokine that has been associated with decreased functional status, lower ejection fractions, higher right atrial pressures, and poorer prognoses in heart failure. Animal research has demonstrated that IL-6 may be higher in brain-dead donors through activation of the IL-6 receptor system.[49] Further work by Birks et al[49] found that unused donor hearts have significantly higher IL-6 mRNA levels in the myocardium; however, unlike with TNF-α, no difference was found in serum IL-6 levels between used donors, unused donors, and heart failure patients.

Procalcitonin (PCT) is a precursor of calcitonin that is systemically released in sepsis. Research has shown increased levels in up to 87% of organ donors. In a study of the relationship between PCT and donor heart suitability, Venkateswaran et al[50] were able to demonstrate that higher baseline PCT levels > 2.0 ng/ml were associated with worse heart function (EF, stroke work index) and less improvement, even after medical therapy. With regards to the relationship between PCT and PGD and death in recipients, Wagner et al[14] found that PCT > 2.0 ng/ml had a very high specificity of 95.8%, but only sensitivity of 50%, for 30-day graft-failure in recipients, with a high odds ratio of 43.8. PCT has also been noted to correlate with other biomarkers, such as cTnI, cTnT (an alternative isoform of troponin), and brain natriuretic peptide (BNP), which themselves have been touted as predictors for early graft failure.

BNP and the BNP precursor N-terminal prohormone BNP (NT-proBNP) are released from myocardium in response to increased wall stress. Currently, they are a diagnostic and prognostic tool for heart failure and correlate with ventricular dilatation, remodeling, dysfunction, failure, and death after myocardial infarction and coronary syndrome. With regards to the relationship between BNP levels and donor heart function, higher BNP levels have been associated with worse cardiac outcomes (EF, pulmonary edema, etc) in stroke patients.[51] Another study found non-accepted donor hearts also tended to have higher BNP and cTnI levels and were older.[52] In that study, elevated donor BNP > 160 pg/ml was able to predict with 89% accuracy poor cardiac performance (defined by cardiac index < 2.2 liters/min/m^2) at 12 days in the recipient and a longer hospital stay. Elevated NT-proBNP levels (>125 pg/ml) have also been found to be a marker of poor hemodynamic function and echocardiographic data across all parameters, including EF, pulmonary wedge pressure, and wall motion scores in potential donors after brain stem death.[53]

SWItch/Sucrose NonFermentable, a matrix-associated, actin-dependent regulator of chromatin subfamily a-like 1 (SMARCAL1), is an intracellular protein that acts as a DNA-dependent adenosinetriphosphatase involved in transcription, DNA repair, and chromatin dynamics. Aharinejad et al[13] found that serum SMARCAL1 concentration was elevated in donors whose organs later developed PGD. Its mRNA expression in LV tissue, both before and after aortic cross-clamp, was also associated with later development of PGD. This difference was not noted in recipient serum concentration. Pre-aortic cross-clamp donor and post-aortic cross-clamp serum SMARCAL1 concentration were noted to be the best markers of PGD risk, with odds ratios of 17.05 and 23.78, respectively. Aside from primary data, no further validation has been published.

A composite of the above biomarkers has been proposed as a better method of predicting PGD. Some evidence shows that a combination may be effective. A study by Nicolas-Robin et al[54] assessed in 63 potential organ donors (brain-dead patients) the accuracy of NT-proBNP and cTnT for an early diagnosis of LV systolic dysfunction. When measurements of these 2 biomarkers were combined, the sensitivity of the test (elevated troponin >0.1 μg/liter, NT-proBNP $>$ 1,700 ng/liter) to predict fractional area change $< 30\%$ (severe disease) was 1.00 compared with the sensitivities of

individual measurements (range, 0.78–0.9). Potapov et al[55] likewise found the combination of PCT and cTnT in donors to be a better predictor of early graft dysfunction in recipients than lone biomarkers. More research is needed in this area to try different combinations.

In summary, there is clear evidence to show that biomarkers are useful in predicting early graft failure. Most of these biomarkers are upregulated by the trauma of brain death in donors, and significant elevation has been shown to be associated with PGD and early death after transplantation. Using combinations of biomarkers appears to be more sensitive and may increase the predictive value.

Pharmacologic and mechanical management of PGD: Pascal Leprince

Before the advent of short-term VAD support and extracorporeal membrane oxygenation (ECMO) after transplant, PGD was likely to be uniformly fatal except for isolated cases where emergency salvage retransplantation was possible. Even this, however, had a dismally poor prognosis. This section will evaluate the literature and current status of management for PGD.

Whether low-dose inotropes, vasodilators, and nitric oxide are considered as a specific treatment for PGD or are merely standard of care after cardiac transplantation is currently unclear. Nevertheless, these agents are generally uniformly used in response to cardiac dysfunction immediately after transplant.

Further medical treatment, however, is less clear. Weis et al[56] reported a case study of 12 patients with PGD from 2006 to 2008 who had received 0.1 μg/kg/min levosimendan, a calcium sensitizer, as adjunctive inotropic support. PGD was defined by an EF of 30% on transesophageal echocardiogram despite inotropic support with epinephrine $>$ 0.1 μg/kg/min and the vasodilator, milrinone $>$ 0.3 μg/kg/min. The patients showed improved parameters of cardiac function (EF, cardiac output) over 48 hours, a rapid reduction of the required doses of inotropic drugs, and no patient required mechanical support. The 30-day survival rate was 93%. The results suggest that levosimendan might be a useful adjunct inotrope in the treatment of patients with PGD after cardiac transplant, although a subsequent 3-year follow-up of this study showed a significantly lower 1-year and 3-year survival rate.[57] In addition, 2 characteristics of levosimendan may limit its use in severe forms of PGD: on one hand, it is a powerful vasodilator that is usually contraindicated in hypotensive states, and on the other hand, its inotropic effect usually takes some hours to develop.[58,59]

D'Alessandro et al[6] retrospectively assessed the use of ECMO temporary support as a treatment for PGD. Between 2000 and 2006, 394 patients underwent cardiac transplant.[6] PDG occurred in 90 patients from this cohort after cardiac transplant, defined as the need for inotrope support with epinephrine $>$ 0.3 μg/kg/min and/or the need for mechanical circulatory support in the immediate post-operative 48 hours. Of these 90 patients, 54 received ECMO, 8 used other assist devices (2 biventricular assist devices, 6 centrifugal RV assist), and 28 were on maximal inotropes alone. Overall, patients with PGD had severely reduced survival at 1 year of 37% compared with 78% for patients without PGD. Of those medically treated (i.e., on maximal inotropes only), survival was 46% (13 of 28). Survival was 25% (2 of 8) for those on mechanical support other than ECMO (biventricular assist devices and RV assists) compared with a survival of 50% (27 of 54) for those on ECMO, which was an improvement compared with the other circulatory support methods. Unpublished data from 2009 to 2011 from the same center revealed improved outcomes with ECMO usage in PGD patients, with an increased weaning rate of 84% and an increased survival of 80% at 30 days and 67% at 1 year in the latest cohort. These data, in combination with previous data,[40] suggest that ECMO is becoming a safer and more effective technique to manage patients with PGD.

A subsequent retrospective trial by Taghavi et al[60] compared ECMO with RVAD for acute RV failure, a feature of PGD. From 1984 to 2003, data for 963 heart transplant patients were assessed in which 28 were found to be in acute RV failure. Of these, 15 were implanted with an RVAD, and 13 with ECMO. Patient survival was similar, but graft survival was markedly improved (7 compared with 1). In addition, retransplantation was less often required (1 compared with 6), and weaning rates were significantly higher (10 compared with 2) in the ECMO group compared with the RVAD group. However, the study was clearly limited by the small numbers of patients.

A retrospective analysis of short-term VAD use after transplantation found that amongst 38 patients from 2003 to 2008 who had been implanted with the CentriMag device (Levitronix, Waltham, MA) for PGD survival was 50% at 30 days and 32% at 1 year.[61] Earlier implantation of the device after transplant appeared to correlate with improved survival, and all survivors were supported with the device for no more than 30 days.

In summary, medical treatment of PGD consists of inotropes and vasodilators, although whether these are considered standard of care after transplantation or specific treatments for PGD is unclear. Levosimendan may be helpful for milder cases of PGD, but mechanical circulatory support is the only effective management for more severe cases, appearing to reduce mortality compared with other treatments. This may involve ECMO or implantation of a VAD. From the data, early intervention and short-term support appears to be associated with improved survival.

Donor management and novel organ preservation methods for the prevention of PGD: Fardad Esmailian

Data from the ISHLT Registry indicate that donor age and ischemic times are among the risk factors for reduced survival. Therefore, reduction of the ischemic time and better preservation of older donor hearts may potentially reduce the incidence of PGD and increase graft and patient survival.

Ex vivo perfusion of the donor heart may potentially avoid the limitation of cold storage by providing warm

blood perfusion to the donor organ.[62] This may result in better preservation of the endothelium integrity and reduce the incidence of coronary artery vasculopathy. Furthermore, the use of such technology may increase the donor heart utilization and weeding out sub-optimal organs. The PROCEED II trial is a prospective, randomized (1:1), multicenter, non-inferiority trial of the safety and efficacy of the organ care system (OCS) compared with standard of care (SOC), which is cold storage of donor hearts.[63] The primary end point is 30-day patient and graft survival. Success criteria are defined by the OCS group being statistically non-inferior to SOC. Secondary end points include incidence of cardiac-related severe adverse effects (SAEs), incidence of biopsy-proven ISHLT grade 2R or 3R rejection, and intensive care unit time.

The interim results were presented at the 33rd Annual Meeting and Scientific Sessions of the ISHLT in April 2013 in Montreal. The analysis included 92 patients (43 OCS and 49 SOC patients) who completed the 30-day follow-up as of December 31, 2012. The groups did not differ with respect to donor demographics, cause of death, and recipient demographics. The total cross clamp-time was longer in the OCS group (5.4 ± 1.4 hours) vs the SOC group (3.4 ± 1.1 hours) because a certain amount of time was spent at the donor hospital to ensure stabilization of the donor heart on the OCS before departure. However, the total ischemic time was significantly lower in the OCS group (1.8 ± 0.4 vs 3.4 ± 1.1 hours, respectively). There were no statistical differences between the 2 groups with respect to 30-day patient survival, 30-day graft survival, all reported SAEs, reported cardiac SAEs, early graft dysfunction, and episodes of rejection. Overall the interim outcome of the OCS donor preservation method appears potentially non-inferior to the SOC method of procurement. Development of more effective donor management and donor heart preservation strategies may reduce the incidence of PGD (Table 3).

Effect of intraoperative blood cardioplegia during heart transplantation and implantation: Florian Wagner

Single cold flush preservation has become the gold standard to protect the heart during transplantation against reperfusion injury and PGD. This method allows reliable protection as long as total ischemic time of the heart does not exceed 3 to 4 hours and donor age is < 40 years.[64] Clinical reality today often challenges these limits due to changes in the donor population and altered non-regional organ allocation. Various methods of controlled reperfusion have been proven experimentally to extend ischemic tolerance of the heart.

Table 3 Preventive Measures to Decrease Incidence of Primary Graft Dysfunction

- Donor management (addition of hormones therapy, lower inotropes)
- Better matching of donor to recipient
- Better preservation (Organ Care System, different additives in solutions)
- Gradual wean of inotropes
- Increase use of nitric oxide
- Decrease ischemic time
- Decrease transfusion requirements
- Improved procurement techniques
- Recipient selection

In this study,[65] the effectiveness of additional intraoperative blood cardioplegia, similar to a protocol proposed by Beyersdorf et al,[66] was analyzed. Between January 2002 and July 2012, 163 heart transplants were performed at the University Heart Center, Hamburg, Germany. In Group 1 ($n = 72$; January 2002–December 2005) donor hearts were preserved with standard filtrated cold University of Wisconsin (UW) single flush perfusion (1000 ml) and served as the historical control. In Group 2 ($n = 49$; January 2006–February 2009) after initial UW preservation, additional Buckberg cold blood cardioplegia was administered antegrade by aortic root after completion of each anastomosis or at least every 20 minutes during implantation. In Group 3 ($n = 42$; March 2009–July 2012), preservation was as in Group 2, but starting with graft implantation, perfusate of extracorporeal circulation blood cardioplegia was leucocyte-depleted by 40×10^{-6} by inline filtration. Primary end point was incidence of PGD, whereas secondary end points included influence of donor/recipient risk factors, ischemic time, and survival.

The results of the study revealed the incidence of PGD was 5.2% in Group 1, 4.1% in Group 2, and 0% in Group 3, ($p < 0.05$ Group 3 vs Group 1). Occurrence of PGD did not correlate with ischemic time, donor age, or size match, and 2 of 6 PGD episodes included female donors. Intraoperative data did not differ significantly between groups with regard to reperfusion time before coming off bypass, primary presence of sinus rhythm, or initial hemodynamic data. Need for inotropic (mean cumulative post-operative dose of epinephrine) and percentage need for IABP support was significantly lower in Group 3 (0.2 vs 0.3 vs. 0.3 μg/kg/min and 2% vs 10% vs 17% in Group 3 vs Group 2 vs Group 1, respectively; $p < 0.05$). Need for permanent pacemaker implantation before hospital discharge was significantly lower in Group 3 (0% vs 2.0% vs 5.5% in Group 3 vs 2 vs 1, respectively; $p < 0.05$). Survival did not differ significantly between groups (85%, 90%, and 91% at 30 days; 78%, 86% and 88% at 1 year in Group 1, Group 2 and Group 3, respectively). From this study, additional intraoperative blood cardioplegia appeared safe and easy to apply. Additional leukocyte filtration significantly reduced the risk of PGD, need for IABP support, and catecholamine dosing despite increased donor risk profile. Safe extension of ischemic times seemed feasible up to 6 hours.

PGD Experience in select transplant centers

The consensus conference also consisted of presentations from high-volume transplant centers regarding their experience and their management of PGD. These are summarized in Table 4. These presentations provided a basis for further

Table 4 Experience from Select Cardiac Transplant Centers: Management of Primary Graft Dysfunction

Transplant center	PGD patients/total cardiac transplants	Clinical approach
	(1/1/2005–1/1/2012)	
Cedars-Sinai Heart Institute[a]	8/555	Cedars-Sinai approach to PGD in the OR 1. Exclude anatomic problems (i.e., anastomosis narrowing or kinking) 2. Maximize inotropic support in the OR with max dose of milrinone (0.5 μg/kg/min), epinephrine (0.08–1 μg/kg/min), and dopamine (5 μg/kg/min). 3. IABP if CI remains $<$ 2.5 L/min/m^2 with CVP and LAP of $>$ 12 mm Hg and MAP $<$ 65 mm Hg despite #2 4. Place on ECMO if CI remains $<$ 2.5 L/min/m^2 with CVP and LAP $>$12 mm Hg and MAP $<$ 65 mm Hg despite #3. Cannulate aorta and right atrium through the chest wall or upper abdominal wall so the sternum can be closed 5. Maintain a cardiac index of 2.5 L/min/m^2 while on ECMO and reduce inotropic support to minimal level so the heart can still eject. 6. Consider placing an LV vent via right superior pulmonary vein or LV apex to decompress the LV or switch the IABP to Impella 2.5 (Abiomed, Danvers, MA) while on ECMO if the heart does not eject. 7. No IV heparin for 24–48 hours. If no bleeding, start heparin to keep ACT at 160–180 8. Reassess myocardial function every 48 hours with TTE in addition to daily hemodynamics 9. If RV or LV improves within 5–7 days, switch ECMO to RVAD or LVAD C-Mag (Levitronix, Waltham, MA) if RV or LV is acceptable; otherwise switch to bilateral C-Mag or TAH, if lung function is acceptable, end organs are still working, and patient is a candidate for redo OHT
Cleveland Clinic[b]	25/350	1. Optimal protection: Intermittent doses of antegrade (root) blood-based cardioplegia every 15–20 minutes. Venting of the LA to avoid heart rewarming. 2. Reperfusion for at least 30 minutes before weaning from CPB. Begin epinephrine (4 μg/min) on all cases. Try to obtain some form of atrial-ventricular conduction. 3. If unable to wean, continue reperfusing for up to a total of 120 minutes. Check for treatable issues such as pulmonary outflow obstruction, narrowed IVC anastomosis, and possible coronary artery issues. Optimize acid/base status. 4. Sort out if this is secondary RV dysfunction from high PVR or RV and or LV dysfunction (i.e., PGD). For former try nitric oxide etc, to reduce PVR. 5. For latter: increase epinephrine to 8 μg/min and add milrinone up to 0.5 μg/kg/min. 6. If unable to wean with sustainable hemodynamics, consider an IABP and prepare for ECMO. 7. Prefer peripheral ECMO to allow chest to be closed and removal at the bedside. 8. Once on ECMO, make sure LA pressure is not elevated. Consider direct measurement of LA pressure. If elevated because of profound LV dysfunction, consider an LA/LV vent. 9. If possible allow RV/LV to eject while on ECMO to reduce the risk of stasis and thrombus formation. 10. Check functional recovery daily with echoes and structured reduction in ECMO flows. 11. Remove ECMO as soon as recovery is enough to safely sustain hemodynamics.
Columbia University[c]	37/573	1. PGD was defined as inability to wean off CPB without the use of an IABP or other mechanical support. 2. 11 of 20 patients received right ventricular support devices (AbioCor [ABIOMED, Danvers, MA] or C-Mag device) used in 11 of 20 patients; 3 patients received BiVAD support; 4 patients LV support and 2 IABPs. 55% of the patients died early in the post-operative period. Of the 45% of patients who could be weaned from mechanical support, long-term outcome was better in those requiring shorter duration of support. 3. Our approach to the management of PGD has evolved: most patients now receive BiVAD support, usually a C-Mag BiVAD with left apical cannulation. 4. More recently ventricular-arterial ECMO has also become a more common mode of support. The median length of device support was 7 days, with an in-hospital mortality of 51%. Only 5.7% survived to re-transplantation.
Johns Hopkins University[d]	20/140	1. LV and root vent on all cases. 2. Drop F_{IO_2} before removing cross clamp.

Continued on page 336

Table 4 *(Continued)*

Transplant center	PGD patients/total cardiac transplants	Clinical approach
		3. 1/2 load of milrinone in young, non-ischemic patients on bypass. 4. HR of at least 100 bpm by atrial pacing or AV sequential pacing. 5. Start with epinephrine to max of 0.1 μg/kg/min. 6. If no improvement, increase epinephrine to 0.15 μg/kg/min max and/or add dopamine or norepinephrine. 7. IABP if looks better, but not great. 8. Nitric oxide if have isolated RV dysfunction. 9. If persistent biventricular or LV dysfunction, resume CPB for at least 30–60 min, then attempt to wean again. 10. If unable to wean proceed to ECMO via existing cannula, preferably after reversing heparin. 11. If isolated RV dysfunction despite nitric oxide (and no anastomotic problems), RVAD only. 12. ECMO the preferred method even with univentricular failure.
University Heart Centre, Hamburg[e]	1/132	1. PGD as the inability to wean from CPB bypass or an early donor heart dysfunction occurring within the first 24 hours after transplant associated with low ejection fraction, low blood pressure requiring major inotropic support and high filling pressures. 2. We diagnose PGD by intra-operative transesophageal echocardiogram, post-operative TTE, right heart catheter (including pulmonary and systemic resistance and cardiac output), central or mixed central or mixed venous saturation and lactate measurements. 3. First step in treatment is inotropic support. 4. Levosimendan works as a positive inotrope by increasing calcium sensitivity of myocytes. Interestingly, there is no adverse effect on relaxation and no increase of oxygen demand of the heart. 5. The second step is the insertion of an IABP as short-term circulatory support (recommend an early insertion). 6. Third step is the implantation of an ECMO, especially in case of pulmonary edema and the possibility of a neurologic evaluation. 7. An interesting and convenient short-term paracorporeal mechanical circulatory support is the Levitronix/C-Mag device. We use it mainly for primary RV failure, but also for LV failure or biventricular failure. 8. Last step in case of good ventilation parameters and neurologic situation is a VAD as long-term mechanical circulatory support. This can be a univentricular or a biventricular device. 9. To prevent PGD, the organ care system (OCS) provides a pulsatile perfusion of the donor heart with warm, oxygenated, nutrient-enriched donor blood. It allows the stabilization and evaluation of marginal donor hearts.

ACT, activated clotting time; BiVAD, biventricular assist device; C-Mag, CentriMag; CI, cardiac index; CPB, cardiopulmonary bypass; CVP, central venous pressure; ECMO, extra-corporeal membrane oxygenation; F_{IO_2}, fraction of inspired oxygen; HR, heart rate; IABP, intra-aortic balloon pump; IV, intravenous; IVC, inferior vena cava; LA, left atrium; LAP, left atrial pressure; LV, left ventricle; LVAD, left ventricular assist device; MAP, mean arterial pressure; OHT, orthotopic heart transplantation; OR, operating room; PGD, primary graft dysfunction; PVR, peripheral vascular resistance; RV, right ventricle; RVAD, right ventricular assist device; TAH, total artificial heart; TTE, transthoracic echocardiogram.

[a]Jignesh Patel, MD, PhD
[b]Nicholas Smedira, MD
[c]Donna Mancini, MD
[d]Stuart Russell, MD
[e]Hermann Reichenspurner, MD, PhD and Alexander Bernhardt, MD

discussion on treatment of PGD and use of inotropic agents and mechanical circulatory support.

Breakout sessions from the PGD consensus conference

Although specific background presentations took place in the morning of the consensus conference, the afternoon was devoted to breakout discussion sessions. The participants were divided into 3 groups to allow for further discussion and interaction. Each group included a mix of cardiologists, cardiac surgeons, pathologists, and immunologists. Clinical issues regarding recognition, management, and prevention of PGD were discussed similarly amongst participants in the 3 groups. All points of consensus were recorded and presented to a reconvened session of all conference participants. Several consensus points were reached.

Table 5 Classification of Graft Dysfunction

1. Primary graft dysfunction (PGD):
   a. PGD-left ventricle (PGD-LV): Includes left and biventricular dysfunction.
   b. PGD-right ventricle (PGD-RV): Includes right ventricular dysfunction alone.
2. Secondary Graft Dysfunction: Occurs when there is a discernible cause for graft dysfunction (e.g., hyperacute rejection, pulmonary hypertension, known surgical complication).

Summary of the consensus statements on PGD

After the breakout sessions, the reconvened conference focused on reaching consensus on salient topics pertaining to diagnosis and management of PGD. The discussion throughout the day had made it clear that standardization of the definition of PGD was one of the most important requirements of the conference. This would allow easier recognition of the phenomenon and communication between clinicians. It was decided that graft dysfunction be distinguished as primary graft dysfunction (PGD) as opposed to secondary graft dysfunction where there is a discernible cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications (e.g., uncontrolled bleeding; Table 5). Importantly, the diagnosis of PGD is to be made within 24 hours after completion of the cardiac transplant surgery. As a result of the large discrepancy between treatment of patients with RV failure and LV failure, it was also decided that PGD first needed to be divided into two entities: PGD-LV, which includes LV and biventricular failure, and PGD-RV alone (Table 6).

Finally, it was decided that a grading system needed to be developed for PGD-LV. The breakout sessions were in agreement that a 3-part grading system would be most successful and would include the descriptors of mild, moderate, and severe. 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 (Table 6). Only adult donors and recipients were discussed; thus, the following consensus statements may not necessarily apply to pediatric heart transplant patients.

Consensus statements

1. Graft dysfunction is to be classified into PGD or secondary graft dysfunction where there is a discernible cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications (e.g., uncontrolled bleeding; Table 5).
2. The diagnosis of PGD is to be made within 24 hours after completion of the cardiac transplant surgery.
3. PGD is to be categorized into PGD-LV or PGD-RV (Table 6).
4. A severity scale for PGD-LV will include mild, moderate or severe grades based on specified criteria (Table 6).

Table 6 Definition of Severity Scale for Primary Graft Dysfunction (PGD)

1. **PGD-Left ventricle (PGD-LV):**	*Mild PGD–LV*: *One* of the following criteria must be met:	LVEF $\leq$ 40% by echocardiography, *or* Hemodynamics with RAP $>$ 15 mm Hg, PCWP $>$ 20 mm Hg, CI $<$ 2.0 L/min/m^2 (lasting more than 1 hour) requiring low-dose inotropes
	Moderate PGD-LV: Must meet one criterion from I *and* another criterion from II:	I. *One* criteria from the following: Left ventricular ejection fraction $\leq$ 40%, *or* Hemodynamic compromise with RAP $>$ 15 mm Hg, PCWP $>$ 20 mm Hg, CI $<$ 2.0 L/min/m^2, hypotension with MAP $<$ 70 mm Hg (lasting more than 1 hour) II. *One* criteria from the following: i. High-dose inotropes—Inotrope score $>$ 10[a] *or* ii. Newly placed IABP (regardless of inotropes)
	Severe PGD–LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP.
2. PGD-right ventricle (PGD-RV):	Diagnosis requires either both i and ii, or iii alone:	i. Hemodynamics with RAP $>$ 15 mm Hg, PCWP $<$ 15 mm Hg, CI $<$ 2.0 L/min/m^2 ii. TPG $<$15 mm Hg and/or pulmonary artery systolic pressure $<$ 50 mm Hg, *or* iii. Need for RVAD

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.

[a]Inotrope score = dopamine ($\times$1) + dobutamine ($\times$1) + amrinone ($\times$1) + milrinone ($\times$15) + epinephrine ($\times$100) + norepinephrine ($\times$100)[67] with each drug dosed in µg/kg/min.

5. Risk factors are categorized in terms of donor, recipient, or surgical procedural factors. Optimization of risk factors and improved allocation and matching of donors and recipients may result in decreased incidence of PGD.
6. Medical management with inotropic support should initially be instituted for PGD. The use of levosimendan may also be helpful. For PGD-RV, nitric oxide and phosphodiesterase inhibitors may be helpful.
7. Mechanical circulatory support of PGD such as ECMO is indicated when medical management is not sufficient to support the newly transplanted graft.
8. Retransplantation for severe PGD may be indicated in select patients if risk factors are minimal.
9. All patients in whom mechanical circulatory support is placed directly into the heart should have a heart biopsy performed at that time.
10. It was recommended that an autopsy should be performed in all patients who are diagnosed with PGD and subsequently expire.
11. Potential future studies include creation of a PGD registry, impact of preservation solutions on PGD, mechanistic studies to understand pathophysiology of PGD, and study of donor management to minimize PGD, among others (Table 7).

Disclosure statement

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Table 7 Potential Future Research

- Creation of registry of PGD patients—will allow characterization of patients under standardized definition
- Mechanistic and pathologic studies to understand the pathophysiology of PGD
- PGD in heart and other organs from that donor
- Studies to assess impact of preservation solutions, surgical techniques and other strategies (ex vivo transport devices)
- Studies to assess pharmacologic and mechanical support in the treatment of PGD to create an evidence-based treatment algorithm
- Cardiotoxic drugs
- Biomarkers to predict PGD, further validation studies of existing biomarkers
- Donor management goals
- Pathology of failed organs (heart biopsy, autopsy)
- Further research into inflammatory cascade that may lead to PGD
- To study the relationship of iron deficiency anemia and incidence of PGD
- Creation of animal model of PGD
- Studies in human brain death

PGD, primary graft dysfunction.

Appendix A. Participants of Consensus Conference

Francisco Arabia, Cedars-Sinai Heart Institute; David Baran, Newark Beth Israel Medical Center; Emma Birks, University of Louisville; Patricia Chang, University of North Carolina; Monica Colvin-Adams, University of Minnesota; Jack Copeland, University of California-San Diego; Lawrence Czer, Cedars-Sinai Heart Institute; Richard Daly, Mayo Clinic/St. Mary's Hospital; Duane Davis, Duke University Medical Center; Teresa DeMarco, University of California-San Francisco; Mario Deng, University of California-Los Angeles; David Dyke, University of Michigan; Howard Eisen, Drexel University College of Medicine; Eric Epailly, Les Hopitaux Universitaires de Strasbourg (France); Fardad Esmailian, Cedars-Sinai Heart Institute; David Feldman, Minneapolis Heart Institute; Arnt Fiane, Oslo University Hospital Rikshospitalet (Norway); Lee Goldberg, University of Pennsylvania; Einer Gude, Oslo University Hospital Rikshospitalet (Norway); Haissam Haddad, University of Ottawa Heart Institute (Canada); Elizabeth Hammond, Latter Day Saints Hospital; Nicola Hiemann, Deutsches Herzzentrum Berlin (Germany); Sharon Hunt, Stanford University Medical Center; Arjun Iyer, Victor Chang Cardiac Research Institute (Australia); Valluvan Jeevanandam, University of Chicago Medical Center; Maryl Johnson, University of Wisconsin; Ingo Kaczmarek, Ludwig Maximilians University (Germany); Anantharam Kalya, Mayo Clinic Hospital; Jon Kobashigawa, Cedars-Sinai Heart Institute; Robert Kormos, University of Pittsburgh Medical Center; Gayathri Kumarasinghe, St. Vincent's Hospital (Australia); Sudhir Kushwaha, Mayo Clinic; Pascal Leprince, La Pitie Hospital (France); JoAnn Lindenfeld, University of Colorado Hospital; Ugolino Livi, S. Maria della Misericordia General Hospital (Italy); Daniel Luthringer, Cedars-Sinai Medical Center; Peter Macdonald, St. Vincent's Hospital (Australia); Donna Mancini, Columbia University; Luigi Martinelli, Ospedale Niguarda (Italy); Mandeep Mehra, Brigham & Women's Hospital; Takeshi Nakatani, National Cerebral and Cardiovascular Center (Japan); David Nelson, Integris Baptist Medical Center; Ivan Netuka, Institute for Clinical and Experimental Medicine (Czech Republic); Maria Paniagua, Hospital Universitario a Coruña (Spain); Jayan Parameshwar, Papworth Hospital (England); Jignesh Patel, Cedars-Sinai Heart Institute; Daniel Pauly, University of Florida; Si Pham, University of Miami/Jackson Memorial Hospital; Sean Pinney, Mount Sinai Medical Center; Barbara Pisani, Rush University Medical Center; Luciano Potena, University of Bologna (Italy); Piotre Przybylowski, Jagiellonian University (Poland); Danny Ramzy, Cedars-Sinai Heart Institute; Hermann Reichenspurner, University Heart Centre Hamburg Eppendorf (Germany); E. Rene

Table B1

Pathologic diagnosis	Autopsy results
	(%)
Rejection	7
Reperfusion injury/ischemia	48
Possible freeze injury	7
Pulmonary embolus	3.4
Myocyte necrosis	28
Antibody-mediated rejection (C4D staining; CD68)	3.4
Multifocal edema and/or hemorrhage	14
Aortic tear	3.4
Infection	3.4

Rodriguez, Cleveland Clinic Foundation; Heart J Ross, Toronto General Hospital (Canada); Stuart Russell, Johns Hopkins Hospital; Gianluca Santise, Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (Italy); Uwe Schulz, Heart Center North-Rhine Westphalia (Germany); Javier Segovia, Hospital de Puerta De Hierro (Spain); Sara Shumway, University of Minnesota; Nicholas Smedira, Cleveland Clinic Foundation; Randall Starling, Cleveland Clinic; Josef Stehlik, University of Utah; David Taylor, Cleveland Clinic Foundation; Hannah Valantine, Stanford University Medical Center; Adrian Van Bakel, Medical University of South Carolina; Florian Wagner, University Heart Center Hamburg Eppendorf (Germany); Shoei-Shen Wang, National Taiwan University (Taiwan); Lori J. West, University of Alberta (Canada); Michel White, Montreal Heart Institute (Canada); George Wieselthaler, University of California-San Francisco; Andreas Zuckermann, Medical University of Vienna (Austria).

Appendix B. Autopsy Results from Survey

See Table B1

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