Chapter

Primary Graft Dysfunction after Heart Transplantation

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Abstract

The entire transplant journey that the donor heart experiences affect the donor heart function early after transplantation. The early graft dysfunction without discernible cause is primary graft dysfunction (PGD) and has been one of the critical complications and the cause of early mortality after orthotopic heart transplantation. Although, numerous researchers investigated the pathophysiology and the related biomarkers, the process is multifactorial and therefore no definite biomarker has been proposed. After the recent definition from the International Society of Heart and Lung Transplantation, the standard of management is still under investigation by each status. Here, the prevalence, pathophysiology, biomarkers, and recent progression of management of PGD will be reviewed.

Keywords: heart transplantation, primary graft dysfunction

1. Introduction

Heart transplantation (HTx) remains the most effective long-term treatment for eligible patients with advanced heart failure. Remarkable improvements in HTx outcomes over decades with advances in medicine and surgical techniques, Primary graft dysfunction (PGD) has been one of the critical complications after orthotopic heart transplantation and cause of early mortality [1, 2]. However, even the definition has formulated recently in 2014, by the International Society of Heart and Lung Transplantation (ISHLT) in the consensus statement and management guidelines are still absent [3]. The 30-day mortality of PGD had been reported with a wide range of 2.3-28.2% in the era before consensus definition. Although, applying new a definition, the early mortality with PGD patients showed no great difference, 6.06-18.4% [4–6].

2. Primary graft dysfunction

2.1 Definition, prevalence, diagnosis

2.1.1 Definition

PGD was defined as any graft dysfunction that occurs within 24 h after completion of transplant surgery (**Table 1**). This definition was established during the annual meeting of ISHLT in 2013. Primary means, not associated with a discernible cause, such as

PGD-left ventricle (PGD-LV)	Mild PGD-LV	One of the following criteria must be met: LVEF ≤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 h) requiring low-dose inotropes
	Moderate PGD-LV	Must meet one criterion from I and another criterion from II: I. Criteria LVEF ≤40%, or Hemodynamic compromise with RAP >15 mm Hg, PCWP >20 mm Hg, CI < 2.0 L/min/m2 Hypotension with MAP <70 mm Hg (> 1 h) II. Criteria. i. High-dose inotropes: Inotrope score > 10* 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.
PGD-right ventricle (PGD-RV)		Diagnosis requires either both i and ii, or iii alone: i. Hemodynamics with RAP >15 mmHg, PCWP <15 mmHg, CI < 2.0 L/min/m^2 ii. TPG <15 mmHg and/or sPAP <50 mm Hg, or iii. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic 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.
**Inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in μg/kg/min.*

Table 1.
Definition of severity scale for primary graft dysfunction [3].

hyperacute rejection, pulmonary hypertension, or uncontrolled intraoperative bleeding requiring massive blood product transfusions and prolonged graft ischemic time [3, 7].

2.1.2 Prevalence and outcomes

Primary graft dysfunction develops fairly common after HTx. A report from two Italian center studies described a 518-patient cohort with a 14% prevalence of PGD and a mortality of 54% in patients with severe PGD [8]. In addition, a UK National study evaluated medical records, PGD developed in 163 among 450 adult heart transplant cohort, and the overall incidence of PGD was 36.2%. The distribution of PGD according to severity was 4, 72, 81 and 6 for mild, moderate, severe LV PGD, and RV. A recently published data from South Korea showed 6.7% (38/570) of incidence, most of them were moderate to severe state (34/38). The early mortality rate in patients with moderate to severe PGD-LV (20.6%) differed significantly from that in patients without PGD (0.6%; $P < 0.001$). From the landmark analysis, the authors showed the strong effect of moderate to severe PGD-LV on early death, and no significant difference in late survival rates (>3mo) in patients with or without moderate to severe PGD-LV.

The outcomes of a different cohort of 191 patients found worse 30-day mortality of 25% in moderate to severe PGD group, the survival curves diverged during the first 3 months following transplantation but went parallel after this initial postoperative period [9]. That means, PGD mainly affects the early deaths, not the late deaths.

The detailed incidence and outcomes of each study is summarized in **Table 2**.

References	Year of publish	Years of data obtained	PGD/Total patient number of cohort (%)	Mild LV PGD	Moderate LV PGD	Severe LV PGD	RV PGD	30-day mortality PGD vs no-PGD	Long-term outcome PGD vs no-PGD
Daronavalli et al.* UK [10]	2015	2007–2011	94/290 (32%)					37.2% versus 4.1%	1-year morality 41.5% versus 8.2%
Sabatino M., et al. [8] Italy	2017	1999–2013	72/518 (14%)	4/72 (5%)	33/72 (46%)	35/72 (49%)		27% versus 3% mild (0%), moderate (12%), severe (65%)	PGD no longer influenced mortality after hospital discharge
Squiers J., et al. [9] USA	2017	2012–2015	59/191 (31%)	35/59 (59%)	8/59 (14%)	16/59 (27%)		mild (0%), moderate (0%), severe (38%) versus 0%	1-year survival:mild (94%), moderate (75%), severe (44%)
Nicoara A. et al. [6] USA	2017	2009–2014	99/317 (31%)					1.7% without VAD 12.8% with VAD versus 0.9%	1-year mortality 15% without VAD 28% with VAD versus 4.1%
Foroutan F. et al. [11] Canada	2019	2004–2015	82/412 (20%)	15/82 (18%)	39/82 (48%)	19/82 (23%)	12/82 (15%)		
Singh S., et al. [5] UK	2019	2012–2015	163/450 (36%)	4/163 (3%)	72/163 (44%)	81/163 (50%)	6/163 (4%)	19% versus 4.5%	6 month mortality 31.9% versus 6.3%
Rhee Y., et al. [4] South Korea	2021	1992–2017	35/570 (6%)	1/35 (3%)	14/35 (40%)	20/35 (57%)	3/35 (8.6%)	mild (0%), moderate (14.3%), severe (25%) versus 0.6%	1-year survival: 72.5 ± 7.5% versus 95.1 ± 0.9%

**Applied PGD criteria within 72 h after transplantation.*

Table 2.
Incidences of PGD according to new ISHLT criteria showed in various reports.

2.1.3 Differential diagnosis with secondary graft dysfunction (SGD)

When it comes to the first facing of PGD, a novice in HTx could have difficulties in differentiating PGD from SGD. SGD has discernible causes such as pulmonary hypertension, surgical complications, or hyperacute rejection [3]. A significant improvement in the pretransplant management of both donors and recipients could contribute to reducing the incidence of SGD over a decade, from10 to 5.6% [8], although there are some differences in the reported incidences [2, 8]. For SGD and PGD share some risk factors and could develop concurrently. Therefore, the patient's condition is unacceptable for the satisfactory evaluation for differential diagnosis, treatment targeting both SGD and PGD is warranted. Several diagnostic pearls and pitfalls are summarized in **Table 3**.

2.2 Pathophysiology

The entire transplant journey that the donor heart experiences including brain death, storage of the organ in a hypothermic environment, potential exposure to warm ischemia, and reperfusion could affect the allograft dysfunction [15]. The surge of catecholamines following brain injury leads to myocardial ischemia, calcium overload, and alteration in the sensitivity of myocytes to calcium. This is further aggravated by exogenous catecholamines following cardiopulmonary bypass and reperfusion [16, 17].

In addition, the ischemia-reperfusion injury (IRI) has been thought to play another major role in the development of PGD. Once the aortic cross-clamp is applied, cold cardioplegia is infused via the aortic root at approximately 4°C. The retrieval process is completed with the heart placed in a cold storage container. The cold storage induces hypothermic arrest of metabolism and maintains viability during this reduced metabolic state, therefore minimizing cellular swelling and reperfusion injury [18]. At these temperatures, and with limited oxygenation, the heart switches from aerobic to anaerobic metabolism. Generally in the hypothermic state (0–4°C), there is a 12-fold decrease in metabolic rate and reduces the accumulation of mitochondrial byproducts of metabolism such as oxygen-free radicals. However, the duration at which the hearts are kept in cold storage matters in the formation of these free radicals. Cellular swelling and lactic acidosis occur in prolonged cold storage, causing an elevation of intracellular H^+ ions [19]. Then, the Na^+/H^+ exchanger is activated resulting in an increase in intracellular Na^+ which activates the Na^+/Ca^{2+} exchanger. The final pathway is the accumulation of cytosolic Ca^{2+} [20]. After releasing cross-clamp, Ca^{2+} overload results in hypercontraction of the myocardium, and a marked rise in end-diastolic pressure with increased ventricular wall stiffness. A greater myofibrillar shortening and cytoskeletal damage occur compared to the ischemic phase [21]. In cellular studies, re-perfused infarcts consist almost exclusively of contraction band necrosis. This process, known as hypercontracture-mediated sarcolemmal rupture (HMSR), impairs Na^+/Ca^{2+} exchanger pumps, and finally increases Na^+ influx into cardiomyocytes via gap junctions and may propagate to adjacent cells [22]. Clinically, the prolonged cold ischemic time of more than 4 h was reported as one of the most important predictors of PGD [23, 24].

2.3 Biomarkers

Several biomarkers have been suggested as potential predictors of PGD, however, the guidelines are absent, and none are in routine use currently.

Secondary graft dysfunction	Incidence	Clinical characteristics	Diagnosis	Management	Prevention
RV failure by Pulmonary hypertension	The most common ~80% [8]	TPG >11 mmHg [12] PVR >2.8WU Young donor heart naïve to high PA pressure	Right heart catheterization RV failure detection by Echo	Inhaled NO (20–40 ppm) IV indicators Volume optimization High FiO_2 for limiting vasoconstriction MCS is needed in hemodynamic instability	Avoid HTx in the recipients with cpcPAH (rather apply LVAD first)
Surgical complications	Second most common	Occlusion of the coronary arteries (dissection, air embolism) Narrowed anastomosis Kinking of the pulmonary artery Significant adhesions >10 Units of packed RBCs	Imaging study (CT, Echo) Events in surgical field Markedly elevated EBL counts	Releasing the mechanical obstructive problems Careful fluid and electrolyte management	Thorough understanding of recipient anatomy and planning via imaging study before surgery
Hyperacute rejection	Very low 01–0.3% [8, 13, 14]	ABO mismatch High DSA with no desensitization	Graft failure within the first few minutes to hours	Inotropes, plasmapheresis, intense immunosuppression (IVIG, rituximab, eculizumab) MCS	Avoid ABO mismatch HTx Prospective cross-matching Desensitization

cpcPAH, combined pre and post pulmonary artery hypertension, CT, computed tomography, DSA, donor-specific antibody, EBL, estimated blood loss, Echo, echocardiography, FiO_2, the fraction of inspired oxygen, HTx, heart transplantation, IVIG, intravenous immunoglobulin, LVAD, left ventricular assisted devices, MCS, mechanical circulatory support, NO, nitric oxide, PA, pulmonary artery, PVR, pulmonary vascular resistance, RV, right ventricle, TPG, transpulmonary pressure gradient.

Table 3.
Brief characteristics of SGD for differential diagnosis with PGD.

2.3.1 Proinflammatory biomarkers in donors and recipients

The pathophysiology of PGD itself is deeply connected with the inflammatory processes after IRI, the related markers were investigated. Tumor necrosis factor-α (TNF-α) is a representative pro-inflammatory biomarker produced by lymphocytes and macrophages [25]. Venkateswaran et al. highlighted poorer biventricular function in donors with elevated levels of TNF-α using serum immunoassays. In the study, the authors also showed higher baseline donor procalcitonin (PCT) levels were related to worse cardiac index and RV and LVEF and demonstrated PCT level of more than 2 ng/mL might be a tool for the usability of donor heart [26]. Wagner et al. also suggested a PCT level of 2 ng/mL as a cut-off value for increasing 30-day mortality and early graft dysfunction after transplantation [27].

Birks and colleagues noted an increased expression of TNF-α in unused donor hearts due to poor function and compared them with donors with good ventricular function (used donors) and patients with advanced heart failure (HF). They also noted IL-6 mRNA expression was 2.4-fold higher in the unused donor hearts than in those used for HTx [28]. This was accompanied by similar changes in the serum and suggests those could be potential biomarkers for PGD.

Hypoxia-inducible factor (HIF)-1 is activated by various growth factors, cytokines, and vascular hormones, which are essential mediators of IRI. HIF-1 is a heterodimeric α, β transcription factor, and potentiates tissue responses to hypoxia [29]. HIF-1 along with the early growth response factor facilitates the transcription of inflammatory cytokines. Aharinejad et al. performed a prospective analysis in 200 heart donors over 7 years and identified HIF-1 as an independent predictor of PGD [30]. They demonstrated a significant increase in HIF-1 levels especially 10 min after reperfusion and were correlated with higher incidences of PGD.

Recently, the pro-inflammatory tendency of recipients rather than donors has been actively focused by investigators. Giangreco et al. reported KLKB1, a serine protease that controls the activation of both inflammation and coagulation in what is known as the kallikrein-kinin system (KKS), as a potential predictor for PGD using gene set enrichment analysis (GSEA) [31]. A classifier utilizing KLKB1 and inotrope therapy outperforms existing composite scores by more than 50%. In the inflammatory response, KLKB1 converts high molecular weight kininogen into bradykinin stimulating the release of nitric oxide and prostacyclin causing vasodilation and increased vascular permeability.

Truby et al. employed high-throughput proteomic profiling related to innate immune activation and inflammation in HTx recipients of pre-transplant serum from HTx recipients to identify relevant biomarkers [32]. Proteomic profiling revealed 9 out of 342 proteins showed statistical significance in the derivation set. When they were tested in the validation set, only CLEC4C (C-Type Lectin Domain Family 4 Member C, a protein marker of plasmacytoid dendritic cells (pDCs),) was significantly associated with PGD. The odd ratio (95% CI) for CLEC4C for PGD was 1.89 ([1.38, 2.64], $p = 1.3 \times 10^{-4}$) in sensitivity analysis combining the derivation and validation sets. Moreover, when the CLEC4C was added to the traditional risk stratification tool such as RADIAL score, they showed a better risk profile. The aforementioned studies identified not only the biomarkers but also the novel pathogenesis of PGD.

2.3.2 Biomarkers for damaged heart

The measurements of serum cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have shown to be sensitive and specific markers of myocardial damage [33].

After SAH, sympathetic nervous system activation and release of norepinephrine from the myocardial sympathetic nerves could result in myocardial damage and troponin elevation [34]. Many systemic complications occur after brain death like myocardial dysfunction, neurogenic stunned myocardium, segmental wall motion abnormalities, stress cardiomyopathy, and these could affect the cardiac function after HTx. Deibert et al. assessed the clinical significance of elevated cTnI levels in patients with non-traumatic subarachnoid hemorrhage and found that an elevated cTnI (≥1.4 μg/l) was a good indicator of LV dysfunction in patients with subarachnoid hemorrhage [35]. However, the cardiac dysfunction in brain death donors was mostly reversible, and larger studies that investigated the association between donor serum troponin level and PGD showed no relevance [36, 37].

BNP and the BNP precursor N-terminal prohormone BNP (NT-proBNP) are released from myocardium in response to increased wall stress. These are the most useful markers utilized in the heart failure field, with significant predictive value on diagnosis and prognosis. The elevated levels of BNP have been identified in heart donors and high levels may distinguish those donors with severely impaired LV systolic function [38]. Elevated NT-proBNP levels (4125 pg/ml) have also been found to be a marker of poor hemodynamic function and echocardiographic data in potential donors after brain stem death [39].

2.3.3 Other biomarkers

Switch/sucrose non-fermentable, a matrix-associated, actin-dependent regulator of chromatin subfamily a-like 1(SMARCAL1) is an intracellular protein that acts as a DNA-dependent ATPase involved in transcription, DNA repair and chromatin dynamics [40]. In 2009, Ahrinejad et al. demonstrated in a cohort of 336 heart donors that SMARCAL1 levels were significant predictors of both short and long-term survival and PGD. Donor serum cutoff of ≥1.25 ng/ml showed 96% sensitivity and 88% specificity for predicting PGD, with corresponding positive predictive and negative predictive values of 83% and 97%, respectively [41]. It seemed SMARCAL1 could play as a potential biomarker before organ selection or donation, however, it has not been widely used in practice till recent days.

The potential biomarkers, related pathophysiology and clinical implications are summarized in **Table 4**.

2.4 Clinically identified risk factors

Numerous variables have been identified as risk factors for PGD. Broadly, they have been categorized in terms of donor, recipient, procurement, surgical procedural and post-operative factors (**Table 5**).

In general, PGD does not come from a single risk factor, rather from multiple or complex interplays of the risk factors. Therefore, a kind of scoring system for PGD would be reasonable to estimate the risk. In 2011, Segovia et al. suggested a risk scoring system called RADIAL for predicting PGD. 'RADIAL' represents 6 multivariate risk factors: Right atrial pressure ≥ 10 mm Hg, recipient Age ≥ 60 years, Diabetes mellitus, Inotrope dependence, Donor Age ≥ 30 years, Length of ischemic time ≥ 240. In a single-center cohort of 621 HTx recipients transplanted from 1984 to 2006, the percentages of PGD were 8.3%, 11.1%, 24% and, 44.4% in the score of 0–1, 2, 3, and ≥ 4 group. The validated score in an external multicenter cohort (698 HTx from 2006 to 2010) was acceptable for risk stratification [50, 52]. However, the transplanted patient

Biomarkers	Source of sample	Pathophysiology	Clinical implication	Clinical application
TNF-α [25–27]	Donor blood (serum)	Pro-inflammatory cytokine produced by lymphocytes and macrophages	High TNF-α levels are associated with donor heart dysfunction	Surrogate indices of donor heart function
Procalcitonin [26, 27]	Donor blood (serum)	Precursor of the hormone calcitonin Proinflammatory marker	PCT >2 ng/mL, worse cardiac index, RV, LV function, increasing 30-day mortality and early graft dysfunction	Donor heart usability
IL-6/IL-6R [28, 42]	Donor myocardium and serum	Proinflammatory cytokine Also exhibit anti-inflammatory effects	2.4-fold higher blood level in the unused donor hearts	Donor heart usability
HIF-1 [29, 30]	Recipient serum after reperfusion Donor myocardium	Heterodimeric α, β transcription factor mediates tissue responses to hypoxia	HIF-1α mRNA expression after ACC in donors and at 10 min following the release of the ACC in the recipient were significant predictors of PGD	PGD risk stratification?
KLKB1 [31]	Pretransplant recipient blood	A serine protease Down regulated in inactivated complement and immune response pathway	Pretransplant KLKB1 + inotrope enhances prediction of PGD	Recipient PGD risk stratification, selection of therapy?
CLEC4C [32]	Recipient serum	A surface marker of pDCs High pDCs may develop the higher risk of interferon and TNF mediated cardiotoxicity	Full clinical model + CLE4C best predicts the risk of PGD	Recipient PGD risk stratification, target therapy for PGD?
Troponin [43, 44]	Donor blood (serum)	Regulatory proteins that control the interaction between actin and myosin Marker of myocardial damage	Increased Troponin was associated with allograft dysfunction Incomplete myocardial preservation	Surrogate indices of donor heart function
BNP [45]	Donor blood (serum)	Increased wall stress of allograft	Donor serum BNP of >160 pg/mL had 89% accuracy to predict poor cardiac performance	Surrogate indices of donor heart function

BNP, brain natriuretic peptide, CLEC4C, C-Type Lectin Domain Family 4 Member C, HIF-1, hypoxia inducible factor-1, KLKB1, Kallikrein B1, PCT, procalcitonin, pDC, plasmacytoid dendritic cells, PGD, primary graft dysfunction, TNF-α, tumor necrosis factor.

Table 4.
Representative potential biomarkers, related pathophysiology and clinical implications.

Factors	Non-modifiable	Modifiable
Donor	• Age [46, 47] • Death from trauma [48] • Cardiac dysfunction • Cardiac resuscitation time • Substance abuse • Left ventricular hypertrophy [49] • Valvular disease • Coronary artery disease	• Sepsis • Inotropic support [50]
Procurement		• Procurement team experience • Cardioplegic solution
Recipient	• Age [50] • Mechanical support [5] • Congenital heart disease • Multiple thoracic operation [2] • Comorbidities (DM, CKD, Liver dysfunction) [5, 50] • Ventilator dependence • Pulmonary hypertension [8] • LVAD bridging [6]	• Amiodarone usage [51] • Infection
Surgery	• Non-cardiac organ donation • Center volume	• Ischemic time [4, 6] • Female to male recipient [5] • Undersized donor (≥30%) [9] • Blood transfusion requirement
Postop management		• Maintain optimal CO • Maintain optimal UO

DM, diabetes mellitus, CKD, chronic kidney disease, CO, cardiac output, UO, urine output.

Table 5.
Known risk factors for the development of primary graft dysfunction.

population bridged by LVAD was relatively low (16/621, 2.6%) in the study. In a recent single-center study, there was a trend toward increased PGD in pretransplant LVAD recipients (40.4% vs. 32.9%, $P = 0.0555$) [6]. The RADIAL score is the only validated scoring system for PGD thus far however, does not have a definitive role in donor selection or predicting PGD for its limited predictive power. The modifiable risk factors should be managed in every transplantation process. Female to male and undersized donors (≥30%) would have better been avoided. Possible infections should be controlled with antibiotics in both donor and recipient. Vasopressors such as vasopressin and terlipressin, are currently recommended as first-line treatment to reduce the noradrenaline requirement [53]. Insulin or thyroid hormone replacement would be helpful in some donors with hyperglycemia and hormone depletion [54, 55]. During procurement, the team should minimize allograft damage and try the best effort to

reduce the ischemic time. Especially, donors with hypertrophied hearts should be kept to a minimum cold ischemic time due to susceptibility to ischemic injury [2].

2.5 Prevention

Patients with significant coronary artery disease, and/or LV hypertrophy, above 55 years are generally classified as marginal donors [56]. To resolve the severe donor shortage problem, many transplant centers accept extended use of marginal donor hearts [56]. Some authors recommend avoiding marginal donor hearts to reduce the risk of PGD [15]. However, for the absolute shortage of donor supply, and the absence of a groundbreaking alternative, utilization of marginal donors would be inevitable. Therefore, making efforts to minimize PGD after utilizing marginal donors seems more rational than just declining them unconditionally.

Proper donor management (hormone therapy, lower inotropes), better matching of the donor to recipient, improved procurement techniques, better organ preservation (Oran Care System, different additives in solutions), gradual wean of inotropes, utilization of nitric oxide, making efforts to decrease ischemic time and transfusion by improving surgical techniques and thorough planning are suggested as prevention [3]. Among them, the ex-vivo perfusion modifies many variables arising in the course of procurement and delivery of allograft. Ex-vivo perfusion may avoid the limitation of cold storage by providing warm blood perfusion to the donor heart [57]. The Harefield Hospital team reported favorable results in their experience using marginal donors with mild LVH with normothermic ex vivo perfusion [58]. In the prospective, multicenter, randomized, clinical investigation of TransMedics Organ Care System (OCS) for Cardiac Use II trial, 130 patients were randomized to ex-vivo donor heart perfusion or standard cold storage and demonstrated no difference in 30-day patient and graft survival rates or serious adverse events.

The development of more effective donor management and donor heart preservation strategies may reduce the incidence of PGD. Each effort to reduce the risk of PGD could make better results when they gather.

2.6 Management

The current definition for PGD is including the treatment options for each status.

By far the treatment of PGD is still primarily supportive care. PGD is initially managed by using inotropic support using catecholamines and phosphodiesterase inhibitors.

2.6.1 Mild to moderate LV PGD

Mild to moderate PGD cases could be treated medically first with inotropes, vasopressors, nitric oxide, and inhaled prostaglandins. If hemodynamics is not able to be improved to a level of adequate organ perfusion, mechanical support is implemented. IABPs may be a first-line device that gives counter pulsation that reduces afterload and improves coronary perfusion pressure, and it can be placed quickly at the bedside. However, it has limited utilization for partial hemodynamic support (maximum 30% increase in cardiac output) in severe graft dysfunction [15].

2.6.2 Severe LV PGD

In patients experiencing severe PGD early after transplantation, mechanical circulatory support other than IABP (by definition) is required to maintain adequate

end-organ perfusion. This involves veno-arterial extracorporeal membrane oxygenator (VA-ECMO) support or implantation of a temporary ventricular assist device (VAD) without oxygenators such as Centrimag (Thoratec Corporation, Pleasanton, CA), TandemHeart (Tandem Life, Pittsburgh, PA), or Impella (Abiomed, Danvers, MA). Choice of the device, the timing of insertion, device configuration, and management differ even among high-volume transplant centers [3].

The incidence differs from report to report, a significant proportion of PGDs develop as biventricular involvement. Therefore, when it comes to severe PGD, MCS that supports both ventricles could be a better choice than a single ventricular support system. Takeda et al. demonstrated improved outcomes with the use of ECMO compared with temporary surgically implanted VAD for severe PGD with retrospective analysis of data collected in Columbia University Medical Center [59].

In general, it is thought that ECMO leads to better results when applied in early cardiogenic shock before multi-organ failure progresses. The forementioned institution adopted an aggressive ECMO approach for patients with evidence of severe PGD in 2015. VA-ECMO support was initiated early in the assessment of graft dysfunction in the immediate perioperative period, often during or immediately after weaning from cardiopulmonary bypass. In-hospital mortality improved from 28% (conservative) to 5% (prompt, $P = 0.083$). Post-transplant survival at 1 year was 67% in the conservative ECMO cohort and 90% in the prompt ECMO cohort ($P = 0.117$). Although, there was no statistical difference in survival rate for 3 yrs., they concluded that a possible mortality reduction in the prompt ECMO after severe PGD could be expected [60]. Regardless of modality, early intervention and short-term mechanical support seem to be associated with improved survival in severe LV PGD.

2.6.3 RV PGD

Currently, available treatment options for postoperative RV failure are optimization of acid-base status, fluid management, intravenous inotropes and vasodilators, and right-sided mechanical support. Inhaled vasodilators are often preferred because of their more direct effect on the pulmonary vasculature [61]. However, treatment options tend to be dependent on physicians or institutional preferences due to the lack of guidelines. Pulmonary vasodilators have been indicated only for the mild form of PGD-RV, with mechanical circulatory support indicated at an early stage for signs of severe PGD-RV [3].

3. Conclusions

PGD is the leading cause of early morbidity following heart transplantation. It is thought to be multifactorial in origin and several risk factors implicated. Researchers for potential biomarkers have been reporting novel predictors and are still ongoing. Prevention with adjusting modifiable risk factors is needed. Treatment options remain supportive with no definitive pharmacological agents identified yet, however, in terms of severe PGDs, timely mechanical circulatory support could reverse the fatal clinical outcome.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1F1A106657312).

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