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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]