ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: Epidemiology, risk factors, and outcomes

Mario Sabatino, MD,[a] Giuseppe Vitale, MD,[b] Valentina Manfredini, MD,[a] Marco Masetti, MD, PhD,[a] Laura Borgese, BSc,[a] Giuseppe Maria Raffa, MD,[b] Antonio Loforte, MD,[a] Sofia Martin Suarez, MD,[a] Calogero Falletta, MD,[b] Giuseppe Marinelli, MD,[a] Francesco Clemenza, MD,[b] Francesco Grigioni, MD, PhD,[a] and Luciano Potena, MD, PhD[a]

From the [a]Heart Failure and Heart Transplant Program, Department of Specialist, Diagnostic, and Experimental Medicine, Policlinico S.Orsola-Malpighi, Alma-Mater University of Bologna, Bologna, Italy; and the [b]Heart Transplant Program, Istituto Mediterraneo per i Trapianti e le Terapie ad Alta Specializzazione (ISMETT), Palermo, Italy.

KEYWORDS:
primary graft dysfunction;
secondary graft dysfunction;
heart transplant;
early death;
ISHLT consensus classification;
organ allocation;
ECMO

BACKGROUND: Primary graft dysfunction (P-GD) is the leading cause of early mortality after heart transplantation (HT). In this 2-center study we analyze outcomes and risk factors of P-GD according to the recent consensus conference classification endorsed by International Society for Heart and Lung Transplantation.

METHODS: We included all adult HTs performed between 1999 and 2013. P-GD was graded as mild, moderate, and severe, according to International Society for Heart and Lung Transplantation recommendations, and analyzed separately from secondary GD. The primary end point was the combined occurrence of in-hospital death or emergency retransplantation.

RESULTS: Early GD was found in 118 of 518 patients (23%), and 72 (13.9%) met the criteria for P-GD. Of these, 4 (5%) were mild, 33 (46%) moderate, and 35 (49%) severe and mostly characterized by biventricular involvement (78%). The end point occurred in 53 patients (10.2%). Overall, GD was a strong predictor of death-graft loss (odds ratio, 15.9; 95% confidence interval, 7.9–33.5; $p < 0.01$), with non-significant worse outcomes in P-GD (37%) vs secondary GD (27%) patients ($p = 0.2$). The study end point was more frequent in severe P-GD patients (65%) than in moderate (12%) or mild (0%; $p < 0.01$). Several known risk factors influenced the risk for P-GD, and the combination of specific donor and recipient risk factors accounted for approximately 22-times increased odds for P-GD. Donor age, recipient diabetes, ischemic time, and post-operative dialysis predicted non-recovery from P-GD.

CONCLUSIONS: Consensus-defined P-GD identifies patients at major risk for early death and graft loss after HT, although the "mild" grade appeared under-represented and clinically irrelevant. The amplified negative effect of donor and recipient factors on P-GD risk underscores the need for appropriate donor-recipient match.

Reprint requests: Luciano Potena, Academic Hospital S.Orsola-Malpighi, Bldg 25, Rm 9, Flr 1, Via Massarenti, 9, 40138 Bologna, Italy. Telephone: +39-051-2144637.
E-mail address: luciano.potena2@unibo.it

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2017.02.014

J Heart Lung Transplant ▮▮▮▮;▮:▮▮▮–▮▮▮

Primary graft dysfunction (P-GD) is a life-threatening complication and represents the leading cause of death in the first 30 days after heart transplantation (HT).[1] Several single-center reports analyzed epidemiology and risk factors for P-GD, resulting in a wide variability of definitions, incidence, mortality, and associated factors, with scarce effect on post-operative management.[2–9] Indeed, definitions and risk scores derived by single-center data are less predictive when validated in multicenter studies.[6,10] To partially overcome this limitation, the International Society for Heart and Lung Transplantation (ISHLT) recently endorsed a consensus conference proposing a unique definition of P-GD, which could facilitate reporting and investigation of modifiable risk factors.[11] However, this definition still needs clinical validation and proofs of its relevance. We therefore designed this 2-center study to investigate the applicability of the ISHLT classification and to identify relevant risk factors, trying to minimize the single-center reporting bias.

Methods

Patient population and data collection

This retrospective study included all consecutive first HTs performed at 2 Italian centers between 1999 and 2013. Multiorgan transplantations and patients aged younger than 16 years or with more than 30% of missing data fields were excluded. The study was approved by Ethical Board of both institutions and was conducted according to local laws and procedures.

Recipient data were retrieved from a prospectively filed Web-secured database and from the hospital electronic repository. Laboratory data were recorded at the time of admission for HT or from the last available data before HT in case of hospitalized recipients. Pre-transplant pulmonary hypertension (PH) was assessed from the right-sided heart catheterization closest to the HT. Post-HT hemodynamic variables were assessed by Swan-Ganz–derived measurements monitored in the intensive care unit. Donor features were retrieved from National Transplant Center online database.

Definitions and study end points

All definitions derive from the ISHLT consensus conference document.[11] Briefly, the diagnosis of GD was restricted to 24 hours after surgery and was based on echocardiographic and/or hemodynamic criteria, as summarized in Table 1. Secondary GD (S-GD) was ruled out based on pathology-proven rejection, clear surgical complications, or hemodynamic parameters. For example, presence of a post-operative transpulmonary gradient $\geq$ 15 mm Hg associated with low cardiac output was considered as GD secondary to PH. GD manifestation was reported as right ventricle (RV), left ventricle (LV), or biventricular, according to echocardiographic findings. Severity grading was based on inotrope score

Table 1 International Society for Heart and Lung Transplantation Diagnostic Criteria and Classification for Primary Graft Dysfunction[a]

PGD-LV	Mild PGD-LV One of the following criteria must be met:	a. LVEF $<$ 40% by echocardiography b. Hemodynamics with RAP $>$15 mm Hg, PCWP $>$ 20 mm Hg, CI $<$ 2.0 liters/min/m^2 (lasting $>$ 1 hour) requiring low-dose inotropes
	Moderate PGD-LV Must meet 1 criterion from I and 1 criterion from II:	I. One criterion from the following i. LVEF $<$ 40% ii. hemodynamic compromise with RAP $>$15 mm Hg, PCWP $>$ 20 mm Hg, CI $<$ 2.0 liters/min/m^2, hypotension with MAP $<$ 70 mm Hg (lasting $>$ 1 hour) II. One criteria from the following: i. High-dose inotropes—inotrope score $>$10[b] 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-RV	Diagnosis requires both i and ii, or iii alone:	i. Hemodynamics with RAP $>$ 15 mm Hg, PCWP $<$ 15 mm Hg, CI $<$ 2.0 liters/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, intraaortic balloon pump; LVAD, left ventricular assist device; LVEF left ventricular ejection fraction; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; PGD-LV, primary graft dysfunction-left ventricle; PGD-RV, primary graft dysfunction-right ventricle; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary gradient.

[a]Adapted from Kobashigawa et al.[11]

[b]Inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100). Each drug dosed in μg/kg/min.