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Prognostic value of the pre-transplant diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension

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BACKGROUND: Although the transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR) are commonly used to differentiate heart failure patients with pulmonary vascular disease from those with passive pulmonary hypertension (PH), elevations in TPG and PVR may not always reflect pre-capillary PH. Recently, it has been suggested an elevated diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient (DPG) may be a better indicator of pulmonary vascular remodeling, and therefore, may be of added prognostic value in patients with PH being considered for cardiac transplantation.

METHODS: Using the United Network for Organ Sharing (UNOS) database, we retrospectively reviewed all primary adult (age $>$ 17 years) orthotropic heart transplant recipients between 1998 and 2011. All patients with available pre-transplant hemodynamic data and PH (mean pulmonary artery pressure $\geq$ 25 mm Hg) were included (n = 16,811). We assessed the prognostic value of DPG on post-transplant survival in patients with PH and an elevated TPG and PVR.

RESULTS: In patients with PH and a TPG $>$ 12 mm Hg (n = 5,827), there was no difference in survival at up to 5 years post-transplant between high DPG (defined as $\geq$3, $\geq$5, $\geq$7, or $\geq$10 mm Hg) and low DPG ($<$3, $<$5, $<$7, or $<$10 mm Hg) groups. Similarly, there was no difference in survival between high and low DPG groups in those with a PVR $>$ 3 Wood units (n = 6,270). Defining an elevated TPG as $>$ 15 mm Hg (n = 3,065) or an elevated PVR $>$ 5 (n = 1,783) yielded similar results.

CONCLUSIONS: This large analysis investigating the prognostic value of DPG found an elevated DPG had no effect on post-transplant survival in patients with PH and an elevated TPG and PVR. J Heart Lung Transplant 2014;33:289–297

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Significant pre-capillary pulmonary hypertension (PH) is a relative contraindication to cardiac transplantation due to the risk of post-operative right heart failure.[1] Clinicians commonly use the transpulmonary gradient (TPG) and

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pulmonary vascular resistance (PVR) to determine the degree of pre-capillary PH and suitability of potential heart recipients.[1] However, these metrics are not perfect surrogates for pulmonary vascular remodeling. In particular, the TPG varies with differences in cardiac output and left atrial pressure, and neither measure clearly differentiates fixed pulmonary vascular remodeling from reversible changes in pulmonary vascular smooth muscle tone.[2–4]

For this reason, acute and chronic vasodilator response is often tested to determine the reversibility of the pre-capillary PH; yet, even when reversibility is demonstrated, post-transplant mortality remains higher than that seen in patients without PH.[5] Because of these limitations, a metric to better differentiate high and low risk among patients with PH is needed. Interest has been growing in using the diastolic pulmonary gradient (DPG), defined as the diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient, as a means to identify those left heart failure patients with clinically significant pre-capillary PH.[4,6] A recent analysis of patients with left heart disease and PH suggested that a TPG $>$ 12 mm Hg and a DPG $\geq$ 7 mm Hg were associated with worse survival compared with a TPG $>$ 12 mm Hg and a DPG $<$ 7 mm Hg .[6] Our purpose was to use the United Network of Organ Sharing (UNOS) database to explore whether differences in DPG define high-risk and low-risk sub-populations among patients with PH being considered for orthotopic heart transplant (OHT).

Methods

Data source

UNOS provided Standard Transplant Analysis and Research (STAR) files with donor-specific data from December 1988 to June 2011. The data set included prospectively collected metrics from all patients who underwent thoracic transplantation in the United States. The current study was granted an exemption by the Johns Hopkins Institutional Review Board because none of the investigators had access to data sets containing protected health information.

Study design

We retrospectively examined all primary, adult (aged $>$ 17 years) OHT patients (1988 to 2011) with a complete set of pre-transplant hemodynamic data, which at minimum included systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output. Only patients with PH (defined as mPAP $\geq$ 25 mm Hg) were included in the analysis. Patients with multiorgan transplants and redo transplants were excluded. Outcomes of interest included survival at 30 days, 1 year, and 5 years.

Statistical analysis

Continuous variables were compared by Student's *t*-test (parametric) or Wilcoxon rank sum test (non-parametric) as appropriate. Categoric variables were compared with chi-square or Fisher's exact test. Receiver operator characteristic (ROC) curves were constructed for DPG, TPG, and PVR to assess their utility in discriminating survivors from non-survivors after transplant. Total area under the curve (AUC) was considered to assess the value of these measures. ROC cut points were defined using the Youden's index. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. A 2-tailed *p*-value of $<$ 0.05 was considered significant. Means are presented with standard deviations. Because the cause of death was not available, a sensitivity analysis was performed to ascertain the effect of cause of death on our findings. All statistical analyses were performed using Stata 12.1 software (StataCorp LP, College Station, TX).

Results

Cohort statistics

From December 1988 to June 2011, 43,494 patients aged $>$ 17 years underwent primary OHT. After excluding 18,041 patients without complete hemodynamic data and 8,642 patients without PH (mPAP $<$ 25 mm Hg), the final study cohort consisted of 16,811 patients.

ROC curve analyses

When considering all patients with PH (mPAP $\geq$ 25 mm Hg), DPG, TPG, and PVR all had poor ability to discriminate survivors from non-survivors, as evidenced by the AUC values near 0.5 (Table 1). The optimal cut points for DPG in those patients with PH and an elevated TPG, PVR, or both, were determined (Table 2). DPG did not discriminate survivors from non-survivors significantly better than chance in any of these groups at any of the 3 time points ($p > 0.05$ for all).

PH with an elevated TPG

Demographic, acuity, and hemodynamic data for patients with PH and a TPG $>$ 12 mm Hg in strata of DPG ($n = 5{,}827$) are presented in Table 3. Given the variable ROC cut points for

Table 1 Survival in Patients With a Mean Pulmonary Artery Pressure $\geq$ 25 mm Hg

Variable	AUC
DPG	
30-day survival	0.52
1-year survival	0.51
5-year survival	0.52
Transpulmonary gradient	
30-day survival	0.54
1-year survival	0.52
5-year survival	0.52
Peripheral vascular resistance	
30-day survival	0.53
1-year survival	0.52
5-year survival	0.51

AUC, area under the curve; DPG, diastolic pulmonary artery pressure–to–pulmonary capillary wedge pressure gradient.