ORIGINAL RESEARCH

Diastolic Pulmonary Gradient as a Predictor of Right Ventricular Failure After Left Ventricular Assist Device Implantation

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***Background*—**Diastolic pulmonary gradient (DPG) was proposed as a better marker of pulmonary vascular remodeling compared with pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG). The prognostic significance of DPG in patients requiring a left ventricular assist device (LVAD) remains unclear. We sought to investigate whether pre-LVAD DPG is a predictor of survival or right ventricular (RV) failure post-LVAD.

***Methods and Results*—**We retrospectively reviewed 268 patients who underwent right heart catheterization before LVAD implantation from 2007 to 2017 and had pulmonary hypertension because of left heart disease. Patients were dichotomized using DPG ≥7 mm Hg, PVR ≥3 mm Hg, or TPG ≥12 mm Hg. The associations between these parameters and all-cause mortality or RV failure post LVAD were assessed with Cox proportional hazards regression and Kaplan–Meier analyses. After a mean follow-up time of 35 months, elevated DPG was associated with increased risk of RV failure (hazard ratio [HR]: 3.30; *P*=0.004, for DPG ≥7 versus DPG <7), whereas elevated PVR (HR 1.85, *P*=0.13 for PVR ≥3 versus PVR <3) or TPG (HR 1.47, *P*=0.35, for TPG ≥12 versus TPG <12) were not associated with the development of RV failure. Elevated DPG was not associated with mortality risk (HR 1.16, *P*=0.54, for DPG ≥7 versus DPG <7), whereas elevated PVR, but not TPG, was associated with higher mortality risk (HR 1.55; *P*=0.026, for PVR ≥3 versus PVR <3).

***Conclusions*—**Among patients with pulmonary hypertension because of left heart disease requiring LVAD support, elevated DPG was associated with RV failure but not survival, while elevated PVR predicted mortality post LVAD implantation. **(*J Am Heart Assoc*. 2019;8:e012073. DOI: 10.1161/JAHA.119.012073.)**

Key Words: left ventricular assist device • pulmonary hypertension • right ventricular failure

Pulmonary hypertension caused by left heart disease (PH-LHD) is the most common form of pulmonary hypertension (PH). PH-LHD presents in 40% to 75% of patients with advanced heart failure (HF) and it is associated with increased risk of morbidity and mortality.[1,2] Recent guidelines have proposed a classification system for PH-LHD that is based on the diastolic pulmonary gradient (DPG) (defined as the difference between invasive diastolic pulmonary artery pressure [dPAP] and mean pulmonary capillary wedge pressure [PCWP]) and it includes 2 groups; isolated postcapillary PH (mean pulmonary artery pressure [mPAP] ≥25, PCWP >15, DPG <7) and combined pre- and postcapillary PH (mPAP ≥25 mm Hg, PCWP >15, and DPG ≥7 mm Hg).[3] DPG has been recently proposed as a better surrogate of pulmonary vascular remodeling compared with the transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR). In particular, the TPG is more influenced by cardiac output and left atrial pressures and PVR is more influenced by pulmonary vascular compliance.[4,5]

In a large single-center study of patients with PH-LHD, a DPG >7 mm Hg has been reported to be associated with a worse prognosis in a subgroup of patients with increased TPG >12 mm Hg.[6] In contrast, a recent retrospective study of patients with PH-LHD found that elevated DPG was not associated with worse survival, whereas elevated TPG and PVR predicted death.[7]

The prognostic value of DPG in patients with end-stage HF undergoing left ventricular assist device (LVAD) implantation remains unclear. Specifically, the outcomes of these patients are critically dependent on right ventricle (RV) function, and

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Clinical Perspective

What Is New?

- Diastolic pulmonary gradient (DPG) is a marker of pulmonary vascular remodeling. Significant pulmonary vascular remodeling increases right ventricular (RV) afterload and imposes risk of RV failure after left ventricular assist device (LVAD) implantation.
- The present study found that among patients with pulmonary hypertension caused by left heart disease requiring LVAD support, elevated DPG was associated with development of RV failure post LVAD.
- The study found that pre LVAD pulmonary vascular resistance, but not DPG, predicts mortality post LVAD implantation.

What Are the Clinical Implications?

- This study highlights the importance of using DPG as a metric to stratify the risk of RV failure in patients undergoing LVAD implantation.
- Further studies are needed to investigate the response of DPG to LVAD therapy and the impact of this response on RV failure and survival.

those who develop RV failure have higher morbidity and mortality.[8,9] Significant pulmonary vascular remodeling imposes risk of right ventricular afterload stress and RV failure thereafter. We proposed that DPG as a surrogate marker of pulmonary vascular remodeling might help to predict survival and RV failure in patients undergoing LVAD support. In this study, we sought to investigate whether pre-LVAD DPG, compared with PVR and TPG, is a predictor of survival and RV failure post-LVAD implantation based on our institutional 10-year experience.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

Our study protocol was approved by the Institutional Review Board of Mayo Clinic College of Medicine. We identified all consecutive adult patients (age ≥18 years) with end-stage HF who underwent right-sided heart catheterization (RHC) before LVAD implantation at the Mayo Clinic in Rochester, Minnesota, between March 2007 and June 2017, and were found to have PH-LHD with mPAP ≥25 mm Hg and PCWP ≥15 mm Hg. All patients were implanted with contemporary continuous-flow LVADs (HeartMate II or HeartMate III [Abbott] or HeartWare HVAD [Medtronic]). Given the retrospective data analysis, informed consent was waived but none of the patients included in the study refused authorization to use their data for research purposes according to Minnesota's law.

According to our clinical practice, patient selection for LVAD as destination therapy or as bridge to heart transplantation (HT) is directed by various factors, and each case is discussed individually in the multidisciplinary selection conference at Mayo Clinic before a final decision is made regarding eligibility for LVAD or other advanced HF therapies. Guidelines-directed considerations are discussed including age, functional capacity, comorbidities, and end-organs function as well as echocardiographic findings, hemodynamic assessment, cardiopulmonary function testing, frailty assessment, and psychosocial evaluation. RHC is a routinely performed study in all candidates. Based on these considerations, a decision is made about whether a patient is eligible for mechanical circulatory support (MCS), HT, or palliative care. Patients who have chronic heart failure and preserved RV function are usually bridged with an LVAD before HT while those with chronic HF and severe biventricular failure are usually treated with inotropes or total artificial heart as bridge to HT. Patients who present acutely with cardiogenic shock may require temporary MCS before proceeding with durable devices or HT. The selection of temporary MCS is also dependent on the cardiac function and hemodynamic parameters. Patients with severe RV dysfunction and elevated right atrial (RA) pressure (and RA/PCWP ratio) despite maximally tolerated inotropes and HF management (with or without intra-aortic balloon pump support) are preferably treated with venoarterial extracorporeal membrane oxygenation at Mayo clinic and are rarely supported with biventricular assist devices (because of higher associated mortality based on our experience with the use of biventricular assist devices), while those with reasonable RV function or with improvement in right filling pressures are treated with intra-aortic balloon pump, Impella, or venoarterial extracorporeal membrane oxygenation if not responsive to maximally tolerated inotropic support.

The determination of severe RV function requiring mechanical support before LVAD consideration is largely determined by a combination of the clinical presentation, echocardiographic findings, and the hemodynamic data obtained from RHC. We exclude patients for LVAD implantation, either as destination or as bridge to HT, if the RV systolic function does not recover and remains severely reduced combined with signs of HF (peripheral edema, hepatic congestion, and worsening renal function) despite aggressive diuresis, inotropes, and MCS devices. Furthermore, patients without overt RV failure but who are at high risk for post-LVAD RV failure are excluded from LVAD therapy. Besides echocardiographic data,

we typically use RA pressure >16 mm Hg, RA/PCWP ratio >0.6, and pulmonary artery pulsatility index (defined as [systolic PA pressure−diastolic PA pressure]/RA pressure) <2 despite diuretic therapy, inotropes, and temporary MCS devices (ie, intra-aortic balloon pump) for predicting RV failure post LVAD. These patients are at extremely high risk of RV failure post LVAD and are generally excluded from LVAD therapy. Though imperfect, different score models are used, particularly when the aforementioned parameters are not definitive, such as the Michigan score and others, for predicting RV failure postoperatively. All patients who required biventricular assist device or total artificial heart implantation were excluded from the current study.

Clinical, Demographic, and Hemodynamic Data

Demographic, clinical, echocardiographic, invasive hemodynamic, LVAD, and laboratory data were retrospectively reviewed and collected. All patients underwent RHC before LVAD implantation. Systemic arterial pressure and heart rate were measured noninvasively. Mean right atrial pressure (mRAP), systolic pulmonary artery pressure (sPAP), dPAP, mPAP, and PCWP were measured with a pulmonary artery catheter. Cardiac output was determined by the Fick method. Stroke volume index (SVI) was calculated by the cardiac index/heart rate×1000. Right ventricular stroke work index (RVSWI) was calculated by the following equation: RVSWI=SVI×(mPAP−mRAP)×0.0136.[10,11]

Definitions and Outcomes

PVR, TPG, and DPG were collected before LVAD implantation and were defined according to the recent guidelines for the diagnosis and management of pulmonary hypertension. TPG was calculated as the difference between mPAP and PCWP. PVR was calculated in Wood units as the difference between mPAP and PCWP divided by the cardiac output. DPG was calculated as the difference between the dPAP and PCWP.[3] The 2 primary outcomes of this study were all-cause mortality and RV failure post LVAD. The patients were followed from time of LVAD implantation until the time of event (death or RV failure), HT, or until the end of the study follow-up period. Survival and RV failure information was obtained from subsequent clinic visits and written correspondence from local physicians.

RV failure post LVAD implantation was defined as elevated RA pressure (>16 mm Hg) accompanied by manifestations of right heart failure, including peripheral edema, ascites, and laboratory evidence of worsening hepatic and/or kidney function, requiring postoperative intravenous inotropic support for >14 days, right-sided circulatory support (RVAD implantation), or hospital discharge on at least 1 inotrope despite aggressive diuresis and maximally tolerated HF medical therapy.[9,10] We used this definition for RV failure post LVAD also supported by echocardiographic data demonstrating at least moderate systolic RV dysfunction in combination with the abovementioned hemodynamic and treatment information.

All patients underwent echocardiography before LVAD implantation, including a detailed assessment of the baseline RV function preoperatively. The severity of RV dysfunction was determined by echocardiography specialists based on the recommendations of the American Society of Echocardiography.[12] A qualitative 4-point score (none, mild, moderate, or severe) was used to describe RV dysfunction. Additionally, quantitative parameters, such as RV end-systolic and end-diastolic volumes, tricuspid annular plane systolic excursion, and RV free-wall longitudinal strain, were generally used to confirm the assessment of RV function observed by the echocardiography reader.

Statistical Analysis

The hemodynamic parameters of interest were presented as continuous variables as well as categorical variables using the clinically important cut points of DPG ≥7 mm Hg, TPG ≥12 mm Hg, and PVR ≥3 Wood units to examine the associations between these parameters and the main clinical outcomes, including all-cause mortality and RV failure events post LVAD. All variables were tested for normal data distribution. Normally distributed continuous variables were presented as means±SD, and non-normally distributed data were presented as the median with the first and third quartiles (Q1, Q3). Categorical variables were reported as number and percent. Patient characteristics were compared between the DPG ≥7 and DPG <7 groups using χ^2 test for categorical variables, Student *t* test for normally distributed continuous variables, and the Mann–Whitney rank sum test for continuous variables with skewed distribution. For multiple groups, 1-way ANOVA and Kruskal–Wallis were used. Kaplan–Meier models were used to estimate survival curves for different groups stratified by DPG, PVR, and TPG and log-rank tests to compare them. To estimate the hazard ratios (HRs) of death or RV failure for DPG, TPG, and PVR groups, a Cox proportional hazards regression model was used with adjustment for relevant clinical, laboratory, and echocardiographic variables including age, sex, body mass index, baseline RV function based on echocardiographic evaluation, and aspartate aminotransferase, total bilirubin, and creatinine levels when analyzing the risk of all-cause mortality, and for age, sex, and baseline RV function when analyzing the risk of RV failure following LVAD implantation. Patients who underwent HT were censored at the time of transplantation. All significance tests were 2 tailed and

conducted at the 5% significance level. All statistical analyses were performed using JMP 9 software (SAS Institute, Inc., Cary, NC).

Results

We identified 268 patients who were evaluated by RHC before LVAD implantation and were found to have mPAP ≥25 mm Hg and elevated PCWP ≥15 mm Hg suggestive of PH-LHD. Of those, 50 (18.7%) patients had DPG ≥7 mm Hg and 218 (81.3%) had DPG <7 mm Hg. Patients with DPG ≥7 mm Hg were younger (55.6 versus 60. 7, *P*=0.01), had improved kidney function (estimated glomerular filtration rate 57.1 versus 47.0, *P*=0.045) but lower rates of LVAD implanted as destination therapy (48.0% versus 66.1%, *P*=0.02). Invasive hemodynamic evaluation showed that patients with DPG ≥7 mm Hg had significantly higher mPAP (44.0 versus 37.5 mm Hg, *P*<0.001), higher PVR (6.1 versus 3.2 Wood units, *P*<0.001), higher TPG (21.5 versus 12.0 mm Hg, *P*<0.001), higher RA/PCWP ratio (0.71 versus 0.57, *P*=0.002), and higher RVSWI (8.6 versus 7.42, *P*=0.04), but had lower PCWP (22 versus 24 mm Hg, *P*<0.001). Echocardiographic parameters obtained at a median (Q1, Q3) time of 11 (5–23) days before LVAD implantation showed that patients with DPG ≥7 mm Hg had higher rates of significant (moderate or more) mitral regurgitation (70.0% versus 52.3%, *P*=0.02). Left ventricular ejection fraction and RV function were similar between the 2 groups (Table 1).

Associations Among Baseline DPG, TPG, PVR, and All-Cause Mortality Post LVAD

After a median (Q1, Q3) time follow-up of 2.2 (0.89–4.30) years, the primary outcome of all-cause mortality occurred in 125 of the 268 patients included in the study (46.6%). Unadjusted Cox proportional hazards showed no significant association between DPG values and incidence of all-cause mortality (HR 1.01; 95% CI, 0.98–1.04 per unit increase in DPG values; *P*=0.460) (Table 2). When stratified into 2 groups based on DPG values, patients with high DPG (≥7 mm Hg) had similar mortality rates compared with those with low DPG (<7 mm Hg) (HR 1.01; 95% CI, 0.63–1.55; *P*=0.97) (Table 2 and Figure 1A). Similarly, increased TPG was not significantly associated with higher all-cause mortality both when analyzed as a continuous variable (HR 1.02; 95% CI, 0.99–1.05 per unit increase in TPG values; *P*=0.203) and when analyzed as high (TPG ≥12 mm Hg) versus low (TPG <12 mm Hg) groups (HR 1.05; 95% CI, 0.73–1.53; *P*=0.787) (Table 2 and Figure 1B). In contrast, PVR was a significant predictor of all-cause mortality post LVAD implantation (unadjusted HR 1.09; 95% CI, 1.02–1.17 per unit increase in PVR; *P*=0.008). Patients with baseline PVR ≥3 Woods unit had significantly higher rates of mortality as compared with those with PVR <3 Woods unit (unadjusted HR 1.65; 95% CI, 1.14–2.44; *P*=0.007) (Table 2 and Figure 1C).

After adjustment for clinically important factors, including age, sex, body mass index, baseline RV function, and aspartate aminotransferase, total bilirubin, and creatinine levels, DPG and TPG remained nonsignificant predictors, while PVR remained an independent predictor of all-cause mortality post LVAD (adjusted HR 1.08; 95% CI, 1.02–1.18 per 1 Wood unit increase in PVR, *P*=0.013). Patients with PVR ≥3 had 1.55-fold increased risk of all-cause mortality compared with patients with low PVR (adjusted HR 1.55; 95% CI, 1.05–2.31; *P*=0.026) (Table 2).

Regarding causes of mortality among the study cohort, we were able to identify a specific cause of death in 115 out of 125 mortality events (92%). We have found that among 28 patients who developed RV failure post LVAD, all-cause mortality occurred in 17 (60.7%) patients, while among those without RV failure mortality occurred in 108 (45%) patients (unadjusted HR 1.6; 95% CI, 0.91–2.58; *P*=0.09). Of the 17 deaths in the RV failure group, there were 11 (64.7%) patients who died as a result of RV failure while the remaining 6 patients died because of other direct events besides having RV failure (infection, pump thrombosis, bleeding issues, or multiorgan failure). Table 3 summarizes the specific causes of death stratified by the baseline hemodynamic parameters of interest DPG (≥7 versus <7), TPG (≥12 versus <12), and PVR (≥3 versus <3 Wood units) (Table 3).

Associations Among Baseline DPG, TPG, PVR, and RV Failure Post LVAD

During follow-up, 28 patients developed RV failure (10.5%). On unadjusted Cox proportional hazards analysis with DPG analyzed as a continuous variable, DPG was significantly associated with RV failure (unadjusted HR 1.10; 95% CI, 1.04–1.15 per unit increase in DPG; *P*=0.002) (Table 2). Moreover, patients with high DPG (≥7 mm Hg) had remarkably increased risk of RV failure compared with those with lower DPG values (unadjusted HR 3.43; 95% CI, 1.59–7.21; *P*=0.002) (Table 2, Figure 2A). There was no significant association between TPG (HR 1.05 per 1 unit increase, *P*=0.084) or PVR (HR 1.13 per 1 unit increase, *P*=0.080) and risk of RV failure post LVAD. This association remained nonsignificant when examining these hemodynamic parameters as categorical variables (HR 1.51, *P*=0.309 for TPG ≥12 versus TPG <12 mm Hg and HR 1.88, *P*=0.118 for PVR ≥3 versus PVR <3 Wood units) (Table 2, Figure 2B and 2C).

A multivariate Cox regression model with adjustment for age, sex, and pre-LVAD RV function per echocardiography resulted in a persistent significant association between DPG

Table 1. Baseline Characteristics of the Study Population

	Overall Cohort (n=268)	DPG ≥7 (n=50)	DPG <7 (n=218)	*P* Value
Age, y	59.7±12.4	55. 6±13.0	60.7±12.1	0.01
Female	56 (21%)	11 (22%)	45 (20.6%)	0.83
BMI, kg/m^2	29.0±5.8	28.8±5.0	29.0±6.0	0.84
ICM	116 (43.3%)	20 (40%)	96 (44%)	0.60
Hypertension	111 (41.4%)	18 (36%)	93 (42%)	0.39
Diabetes mellitus	101 (37.7)	21 (42%)	80 (36.6%)	0.45
Atrial fibrillation	127 (47.4%)	25 (50%)	102 (46.8%)	0.68
HeartMate II	204 (76.1%)	34 (68%)	170 (78.0%)	0.31
Days of support, d	776.7±732.31	781.0±768.1	775.8±725.7	0.97
Device as DT	168 (62.7%)	24 (48%)	144 (66.1%)	0.02
INTERMACS score	3 (2–4)	3 (2–4)	3 (2–4)	0.50
Cr, mg/dL	1.5±0.59	1.37±0.60	1.47±0.59	0.26
eGFR, mL/min per 1.73 m^2	48 (36.4–60)	57.1 (38–65)	47 (36–60)	0.05
Bilirubin, mg/dL	1.1 (0.8–1.7)	1.1 (0.7–1.75)	1.1 (0.8–1.68)	0.73
AST, IU/L	32 (24.5–44)	31 (23–39)	33 (25–47)	0.63
ALT, IU/L	28 (19–40)	25 (18.5–38.5)	29 (19.3–40.8)	0.66
Albumin, g/dL	3.8 (3.4–4.1)	3.9 (3.4–4.3)	3.8 (3.5–4.1)	0.90
Hemodynamics				
mAP, mm Hg	76.7 (70.3–82.7)	75.8 (58.3–84.3)	77 (71–82)	0.48
HR	75 (68–86)	79 (69–91)	74 (68–84.5)	0.12
mRAP, mm Hg	14 (11–20)	17 (11–21)	14 (10.5–19)	0.12
sPAP, mm Hg	54 (45.3–62)	62 (53.5–72)	51 (45–60)	<0.001
dPAP, mm Hg	26 (23–31)	33.5 (29–38)	25.5 (22–29)	<0.001
mPAP, mm Hg	38 (33–43)	44 (38–49.3)	37.5 (32–41)	<0.001
PCWP, mm Hg	24 (21–28)	22 (19–27)	24 (21–28)	<0.001
CO, L/min	3.6 (2.9–4.4)	3.51 (2.8–4.4)	3.67 (2.92–4.41)	0.46
CI, L/min per m^2	1.8 (1.4–2.2)	1.8 (1.5–2.1)	1.78 (1.4–2.2)	0.63
PVR, Wood units	3.5 (2.5–5.1)	6.1 (4.4–8.0)	3.2 (2.25–4.32)	<0.001
TPG, mm Hg	13 (10–17)	21.5 (17–27)	12 (9–14)	<0.001
DPG, mm Hg	2 (0–5)	9 (8–13.3)	1 (−1 to 3)	<0.001
RA/PCWP	0.58 (0.44–0.81)	0.71 (0.53–0.95)	0.57 (0.42–0.76)	0.002
RVSWI	7.7±3.7	8.6±3.4	7.42±3.76	0.04
Echocardiography				
LVEF, %	19.1±8.3	17.8±7.6	19.42±8.46	0.19
LVEDD, mm	72.1±30.3	72.4±12.1	72.0±33.17	0.88
RV function				0.47
Moderate	87 (32.5%)	18 (36%)	69 (31.65%)	
Moderate-to-severe	35 (13.1%)	5 (10%)	30 (13.76%)	
Severe	40 (14.9%)	10 (20%)	30 (13.76%)	
Significant TR*	152 (56.7%)	29 (58%)	123 (56.42%)	0.84
Significant MR*	149 (55.6%)	35 (70%)	114 (52.29%)	0.02
Significant AR*	9 (3.4%)	2 (4%)	7 (3.21%)	0.78

Values are presented as n (%), mean±SD or median (interquartile range). ALT indicates alanine transaminase; AR, aortic regurgitation; AST, aspartate aminotransferase; BMI, body mass index; CI, cardiac index; CO, cardiac output; Cr, creatinine; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary gradient; DT, destination therapy; eGFR, estimated glomerular filtration rate; HR, heart rate; ICM, ischemic cardiomyopathy; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; mAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; mRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; SPAP, systolic pulmonary artery pressure; TPG, transpulmonary gradient; TR, tricuspid regurgitation.
*Moderate or more in severity.

Table 2. Associations of DPG, TPG, and PVR With Risk of Death and Right Ventricular Failure

	Death			RV Failure		
	Events No./Total No. (%)	HR (95% CI)	*P* Value	Events No./Total No. (%)	HR (95% CI)	*P* Value
DPG	125/268			28/268		
Per unit increase						
Unadjusted		1.01 (0.98–1.04)	0.460		1.10 (1.04–1.15)	0.002
Adjusted		1.02 (0.99–1.05)	0.195		1.09 (1.03–1.15)	0.002
≥7 vs <7						
Unadjusted		1.01 (0.63–1.55)	0.97		3.43 (1.59–7.21)	0.002
Adjusted		1.16 (0.71–1.82)	0.541		3.30 (1.49–7.11)	0.004
TPG	125/268			28/268		
Per unit increase						
Unadjusted		1.02 (0.99–1.05)	0.203		1.05 (0.99–1.10)	0.084
Adjusted		1.02 (0.99–1.05)	0.211		1.05 (0.99–1.11)	0.080
≥12 vs <12						
Unadjusted		1.05 (0.73–1.53)	0.787		1.51 (0.69–3.65)	0.309
Adjusted		1.05 (0.71–1.52)	0.838		1.47 (0.66–3.57)	0.352
PVR	125/268			28/268		
Per unit increase						
Unadjusted		1.09 (1.02–1.17)	0.008		1.13 (0.98–1.26)	0.080
Adjusted		1.08 (1.02–1.18)	0.013		1.12 (0.98–1.27)	0.088
≥3 vs <3						
Unadjusted		1.65 (1.14–2.44)	0.007		1.88 (0.86–4.53)	0.118
Adjusted		1.55 (1.05–2.31)	0.026		1.85 (0.84–4.50)	0.130

For right ventricular failure events, adjustment was performed for age, sex, and baseline right ventricular function per echo. For all-cause mortality events, adjustment was performed for age, sex, body mass index, and baseline creatinine, aspartate transaminase, total bilirubin levels, and baseline right ventricular function per echo. DPG indicates diastolic pulmonary gradient; HR, hazard ratio; PVR, pulmonary vascular resistance; RV, right ventricle; TPG, transpulmonary gradient.

and risk for RV failure post LVAD both when DPG was examined as a continuous variable (adjusted HR 1.09; 95% CI, 1.03–1.15 per 1 unit increase in DPG; *P*=0.002) as well as a categorical variable (adjusted HR 3.30; 95% CI, 1.49–7.11 for DPG ≥7 versus DPG <7 mm Hg; *P*=0.004). Similar to the univariate analysis, there was no significant association between TPG and RV failure risk both when examined as a continuous variable (HR 1.05, *P*=0.080) and as a categorical variable using the same cut points described above (HR 1.47, *P*=0.352), nor was there an association between PVR and RV failure (HR 1.12, *P*=0.088, and HR 1.85, *P*=0.130, respectively) (Table 2).

Discussion

In the present study, we reviewed our 10-year experience in a cohort of 268 patients with end-stage HF and PH-LHD who underwent LVAD implantation, seeking to assess the ability of pre LVAD DPG to predict mortality or RV failure after LVAD implantation. We found that elevated DPG was associated with development of RV failure but was not an independent predictor of survival. Conversely, elevated PVR was associated with decreased survival but not with RV failure, whereas elevated TPG was neither an independent predictor of survival nor of RV failure when these hemodynamic parameters were both analyzed as continuous as well as categorical variables.

The gradient between (dPAP) and (PCWP) was previously suggested as an index of pulmonary vascular remodeling, and a cutoff of 7 mm Hg has been previously proposed for clinical use as a surrogate metric for combined postcapillary and precapillary pulmonary hypertension.[3] However, previous studies have shown conflicting results regarding the prognostic value of DPG in patients with PH-LHD. A previous study by Gerges et al[6] suggested that DPG >7 mm Hg was associated with a worse prognosis and in a subgroup of patients with increased TPG >12 mm Hg.[6] In contrast, in a recent retrospective study of patients with PH-LHD that investigated similar cut points of DPG, an elevated DPG was not found to be associated with worse survival at any of the explored levels.[7] However, no patients with end-stage HF requiring LVAD implantation were included in those studies. A

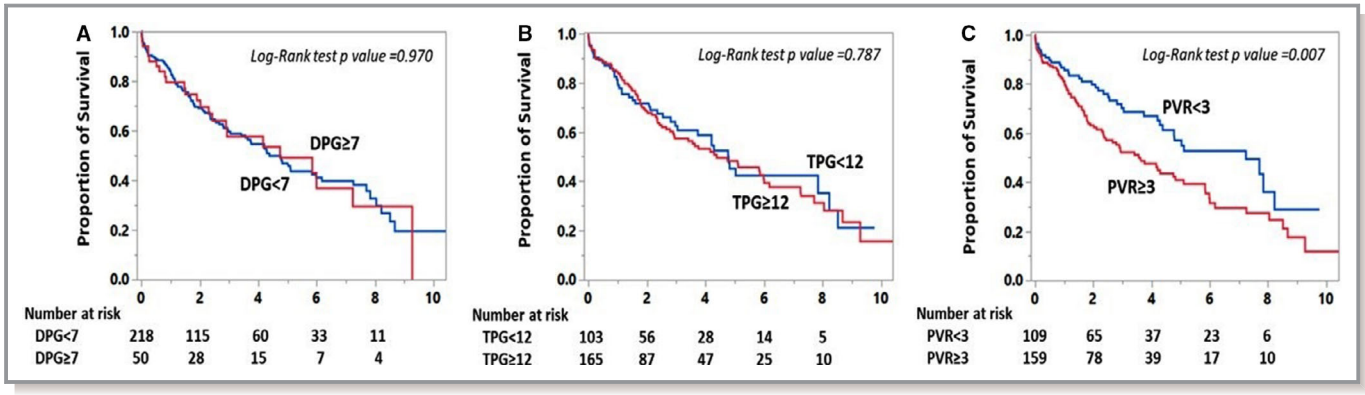

Figure 1. Kaplan–Meier analyses of survival curves stratified by higher and lower DPG (**A**), TPG (**B**), or PVR (**C**). DPG indicates diastolic pulmonary gradient; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

previous small cohort study of 69 patients demonstrated significant decline in DPG after LVAD implantation.[13] This decline may partially account for the inability of DPG to predict survival in our cohort. However, a recent cohort study that investigated the effect of LVAD on DPG in 116 end-stage HF patients with PH-LHD highlighted that despite the DPG decline after LVAD therapy, it remained significantly elevated (>7 mm Hg) in 42% of these patients. DPG >8 mm Hg was found to be significantly associated with nonresponse to LVAD therapy; however, the impact of these findings on outcomes remained unclear.[14] Interestingly, 2 recent studies by Imamura et al demonstrated that the decoupling between diastolic pulmonary artery pressure and pulmonary artery wedge pressure >5 mm Hg at incremental LVAD speeds is associated with worse prognosis following LVAD implantation.[15,16]

We found that elevated PVR ≥3 pre-LVAD implantation predicted worse survival following LVAD. Previous studies have demonstrated that LVAD implantation can normalize PVR by unloading the left ventricle, reducing filling pressures, and augmenting cardiac output. Patients whose elevated PVRs were normalized by LVAD had post-HT survival rates comparable to those without PH. However, these were small cohorts that included various types of LVAD including both pulsatile and continuous flow devices.[17,18] In contrast, Tsukashita et al have recently shown in a large cohort that in-hospital mortality following HT was higher in patients with pre-LVAD PVR ≥5 Wood units compared with those with lower PVR, despite the elevated PVRs being normalized following LVAD implantation. They speculated that unknown indices of PH might still exist and affect posttransplant outcome.[19] In our cohort, TPG ≥12 was not found to be an independent predictor of survival. As compared with TPG, PVR may be a superior prognostic discriminant because it includes flow assessment.[5]

We found that >10% of our patients were complicated by RV failure, with similar rates being reported previously.[20,21]

Table 3. Causes of Mortality Stratified by the Baseline Hemodynamic Parameters Before LVAD Implantation

	Total Events, n (%)	RVF, n (%)	ICH, n (%)	Ischemic Stroke, n (%)	GIB, n (%)	MOF, n (%)	Infection, n (%)	Cancer, n (%)	Arrhythmia, n (%)	Pump Thrombosis, n (%)	LVAD Malfunction, n (%)
DPG, mm Hg											
DPG≥7 n=50	24 (48)	3 (6)	4 (8)	0	0	8 (16)	2 (4)	0	0	1 (2)	1 (2)
DPG<7 n=218	101 (46.3)	8 (3.7)	18 (8.3)	1 (0.5)	6 (2.8)	36 (16.5)	11 (5)	5 (0.9)	2 (2)	3 (1.4)	1 (0.5)
TPG, mm Hg											
TPG≥12 n=165	81 (49.1)	7 (4.2)	14 (8.5)	0	3 (1.8)	29 (17.5)	8 (4.8)	3 (1.8)	0	2 (1.2)	1 (0.6)
TPG<12 n=103	44 (43.7)	4 (3.9)	8 (7.8)	1 (1)	3 (2.9)	15 (14.6)	5 (4.9)	2 (1.9)	2 (1.9)	2 (1.9)	1 (1.9)
PVR, Wood units											
PVR≥3 n=159	85 (53.5)	8 (5)	14 (8.8)	1 (0.6)	3 (1.9)	31 (19.5)	8 (5)	4 (2.5)	2 (1.3)	2 (1.3)	1 (0.6)
PVR<3 n=106	40 (37.7)	3 (2.8)	8 (7.5)	0	3 (2.8)	13 (12.3)	5 (4.7)	1 (0.9)	0	2 (1.9)	1 (0.9)

DPG indicates diastolic pulmonary gradient; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; LVAD, left ventricular assist device; MOF, multiorgan failure; PVR, pulmonary vascular resistance; RVF, right ventricular failure; TPG, transpulmonary gradient.

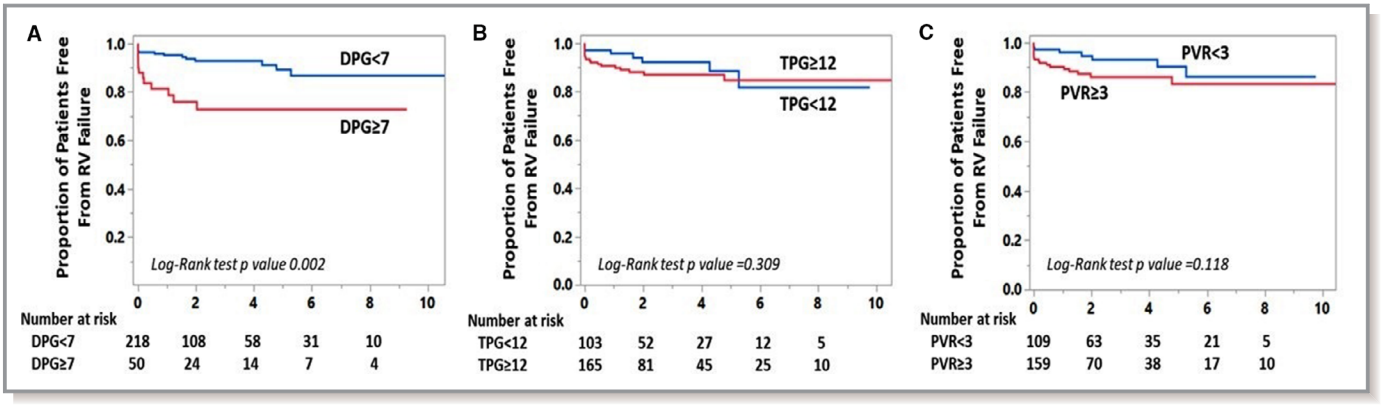

Figure 2. Kaplan–Meier analyses of event-free curves for the occurrence of RV failure stratified by higher or lower DPG (**A**), TPG (**B**), or PVR (**C**). DPG indicates diastolic pulmonary gradient; PVR, pulmonary vascular resistance; RV, right ventricular; TPG, transpulmonary gradient.

Elevated pre LVAD DPG remained an independent predictor of RV failure after adjusting for previously identified factors associated with RV failure.[10] DPG predicted RV failure in all commonly used cut points explored, whereas PVR ≥3 or TPG ≥12 were not associated with RV failure risk. DPG was proposed as a better marker of pulmonary vascular remodeling and less affected by cardiac output, left atrial pressure, and pulmonary arterial compliance than TPG or PVR. The physiological rationale for DPG is based on the expectation that by late diastole, the pressure gradient or difference between the pulmonary artery and left atrium should be minimal.[5] Moreover, patients with DPG >7 mm Hg have been shown to have increased mortality rates as compared with patients with lower DPG values.[6] In 18 of these patients, lung tissue was evaluated and patients with elevated DPG had advanced remodeling of the pulmonary vasculature. The association between RV failure and DPG in different cut points including <7 mm Hg implies irreversible pulmonary vascular dysfunction that further imposes the risk of right ventricular afterload stress and post-LVAD RV failure. In line with our findings, PVR was not found to be an independent predictor of RV failure in a previous study including 245 patients supported by an LVAD.[22] We therefore speculate that the mechanism of RV failure secondary to elevated DPG relates to the presence of irreversible pulmonary vascular remodeling. Therefore, chronic left ventricular unloading may not elicit enough changes in the pulmonary vasculature to decrease pulmonary resistance enough to improve RV function following LVAD implantation. In our study cohort, the separation of RV failure and mortality is not unexpected as mortality in these very sick patients with advanced HF undergoing major surgery and subsequently supported by an LVAD (which is also associated with high risk of life-threatening complications) is still relatively high. Therefore, mortality among this population can be attributed to multiple LVAD and other heart failure–related complications, such as respiratory failure, life-threatening arrhythmias, infection, bleeding issues, pump thrombosis, stroke, and others. Though RV failure is associated with increased risk of mortality post LVAD, it is obvious that not all mortality events can be explained by RV failure, and this separation can result from high mortality incidence caused by multiple factors combined with a relatively low number of RV failure events seen in the overall cohort.

We acknowledge that our retrospective study has several limitations. First, the DPG measurement may be susceptible to technical errors; in particular, the measurement of dPAP is prone to error from catheter motion artifacts. Second, post LVAD hemodynamic data were not available in our cohort. In particular, the changes in DPG, PVR, and TPG following LVAD therapy and the impact of the change in these parameters on clinical outcomes are unclear. Moreover, our study represents the experience of a single center, with the majority of patients implanted with a HeartMate II LVAD as destination therapy, and thus, results might not be generalizable to patients undergoing support with other devices. Lastly, we acknowledge that many statistical tests were performed without adjustment, resulting in possible type 1 errors. Despite this, given the sample size of our study, we feel that sufficient evidence is provided for clinical relevance. Nevertheless, further studies are needed to confirm or refute our results. However, despite these limitations, the large sample size of this study and the complete data set of hemodynamic parameters as well as the long follow-up period enabled us to identify pre-LVAD DPG as an independent predictor of RV failure and pre-LVAD PVR as an independent predictor of all-cause mortality among patients with PH-LHD undergoing LVAD implantation.

Conclusions

Elevated DPG was associated with development of RV failure but was not an independent predictor of survival. Conversely,

elevated PVR was associated with decreased survival but not with RV failure risk. This study highlights the importance of using DPG as a metric to stratify the risk of RV failure in patients undergoing LVAD implantation. Future studies are needed to investigate the response of DPG to LVAD therapy and the impact of this change on clinical outcomes.

Disclosures

None.

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