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ORIGINAL ARTICLE

Pre-operative pulmonary artery pulsatility index does not predict mortality post-cardiac transplantation

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Abstract

Aims The pulmonary artery pulsatility index (PAPi) is a novel haemodynamic marker that has previously been shown to predict right ventricular dysfunction and mortality in patients with pulmonary hypertension and advanced heart failure. Utility of the PAPi in predicting outcomes post-cardiac transplantation is unknown. The aim of this study was to compare the prognostic significance of PAPi against pulmonary vascular resistance (PVR) for the predication of morbidity and all-cause mortality post-transplantation.

Methods and results All patients who underwent cardiac transplantation over a 6 year period were studied. Pre-operative right heart catheter data was obtained. The PAPi was calculated as follows: (systolic pulmonary artery pressure [sPAP] − diastolic pulmonary artery pressure [dPAP])/right atrial (RA) pressure. One hundred fifty-eight patients with a mean age of 49 ± 14 years were studied (43 with a pre-transplant left ventricular assist device [LVAD]). Three patients were excluded due to missing data. In the non-LVAD group, there was no significant difference in PAPi or PVR, nor was there any association with post-operative outcome (including stratification by natural history sub-type; all $P > 0.05$). In the LVAD group, there was no association with PAPi and post-operative outcome; however, PVR was predictive of post-operative mortality (mortality: 2.8 ± 1.3 WU vs. alive: 1.7 ± 0.7 WU; $P = 0.005$).

Conclusions The PAPi was not able to discriminate mortality outcomes for patients post-cardiac transplantation. Pulmonary vascular resistance remains a marker of mortality in an LVAD cohort bridged to transplant (central illustration).

Keywords Left ventricular assist device; Pulmonary artery pulsatility index; Pulmonary vascular resistance; Right heart catheterization; Heart failure

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Introduction

Invasive haemodynamic indices are often used in the setting of advanced heart failure and pulmonary hypertension (PH) to predict adverse outcome. Existing indices to predict right heart failure (RHF) measure either right ventricular (RV) function (including the right ventricular stroke work index [RVSWi]) or pulmonary artery (PA) steady-state load (including pulmonary vascular resistance [PVR]). These indices in isolation may overlook complexities of the right heart system that include the systemic venous return and pulsatile load of the PA circulation (including pulmonary capacitance and impedance). The pulmonary artery pulsatility index (PAPi) is a novel haemodynamic marker that has been shown to be a strong predictor of RHF and mortality in patients with advanced heart failure and pulmonary hypertension.[1] Its utility as a prognostic indicator in patients with advanced heart failure undergoing cardiac transplantation is currently unknown.

The PAPi is derived from invasive right heart catheterization (RHC). It is estimated as the ratio of pulmonary artery

pulse pressure (PAPP) to right atrial pressure (RAP) and expressed as

$$\mathrm{PAPi} = (\mathrm{PASP} - \mathrm{PADP})/\mathrm{RAP},$$

where *PASP* represents pulmonary artery systolic pressure, *PADP* represents pulmonary artery diastolic pressure, and *RAP* represents right atrial pressure. The physiological basis for PAPi as an indicator of RHF is predicated on the fact that PASP is an indirect indicator of RV contractile function against a given afterload, and that a high RAP is a sign of a failing ventricle.

Although the calculation for PAPi is relatively simple, the physiological interpretation of this index is expected to vary significantly in different patient populations based on the underlying pathophysiology.

The aim of this study therefore was to determine the prognostic significance of pre-operative haemodynamic assessment of PAPi against PVR in predicting mortality post-cardiac transplantation in patients with advanced heart failure with or without a left ventricular assist device (LVAD).

Methods

Study population

This was a single-centre, registry study of all patients who underwent cardiac transplantation over a 6 year period at our specialized heart failure and transplantation institution. Inclusion criteria for the study were (i) pre-operative RHC prior to cardiac transplantation, (ii) availability of 3 year cardiovascular morbidity and mortality outcome data. Exclusion criteria included: (i) incomplete or missing RHC data; or (ii) RHC data acquired more than 3 months prior to transplantation; (iii) missing cardiovascular morbidity or mortality data. Patients with a transpulmonary gradient (TPG) $>$ 12 mmHg were not routinely considered for isolated cardiac transplantation at our institution.

Three patients were excluded due to incomplete or missing RHC data. One hundred and fifty-eight patients underwent cardiac transplantation and were enrolled, of which 43 had LVAD insertion prior to transplantation. Natural history prior to transplantation was studied in the 115 patients who did not have bridging LVAD. Dilated cardiomyopathy included idiopathic, viral, and drug-mediated causes. Ischaemic cardiomyopathy included prior history of myocardial infarction, percutaneous coronary artery intervention, or coronary artery bypass surgery. Infiltrative cardiomyopathy included patients with acute right ventricular cardiomyopathy, amyloidosis, hypertrophic cardiomyopathy, sarcoidosis, and other unspecified infiltrative states. Valvular cardiomyopathy included patients with more than moderate to severe stenosis or regurgitation independent of other causes. All remaining patients were assigned to the other group. Informed consent was obtained from each patient prior to RHC as per local hospital protocol, and the study protocol conformed to the local hospital ethical guidelines. All demographic data were manually extracted from the electronic medical records.

Haemodynamic data

Right heart catheterization (RHC) data were routinely collected pre-operatively by a proceduralist blinded to data interpretation. Collected parameters included right atrial (RA) pressure, PA systolic pressure (PASP), PA diastolic pressure (PADP), mean PA pressure (MPAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI), and stroke volume index (SVI) from which transpulmonary gradient (TPG), PVR, and PAPi were derived. The trans-pulmonary gradient was calculated as

$$\mathrm{TPG} = \mathrm{MPAP} - \mathrm{PAWP},$$

where *TPG* represents transpulmonary gradient, *MPAP* represents mean pulmonary artery pressure, and *PAWP* represents pulmonary arterial wedge or capillary pressure and was expressed as mmHg.

Pulmonary vascular resistance was calculated as

$$\mathrm{PVR} = (\mathrm{MPAP} - \mathrm{PAWP})/\mathrm{CO},$$

where *MPAP* represents mean pulmonary artery pressure, *PAWP* represents pulmonary artery wedge or capillary pressure, *CO* represents cardiac output and was expressed as Wood Units (WU). As mentioned previously, the PAPi was calculated as the ratio of pulmonary arterial pulse pressure to RA pressure and expressed as an overall score.

Statistical analysis

All data were manually entered by an independent observer and reported as mean ± standard deviation (SD). A repeated-measures analysis was conducted comparing measures across time. After identification of an overall significant difference, all possible pairwise comparisons were made. A Fisher's exact test and Mann–Whitney *U* test were used to compare descriptive statistics. Data analysis was performed with SPSS-26 (IBM Corporation, Armonk, New York, USA).

Results

A total of 158 patients were studied. The mean age of the study population was 48.6 ± 13.5 years with 48 (30%) females and 110 (70%) males ($P < 0.001$). Sixty-three per cent (72/115) of patients had an underlying dilated cardiomyopathy, 15% (17/115) an ischaemic cardiomyopathy, 19% (22/115)

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an infiltrative cardiomyopathy, 3% (3/115) had primary valvular heart disease, whereas 1 (1/115, <1%) patient was a redo transplant and assigned to the other group (*Table 1*). Forty-three (43/115, 27%) patients underwent bridging LVAD prior to transplantation.

All patients were New York Heart Association (NYHA) functional classes III or IV with severe left ventricular (LV) dysfunction (LV ejection fraction ≤35%) on transthoracic echocardiography at baseline. As demonstrated in *Table 1*, there were no significant differences in intra-operative considerations except for redo median sternotomy rates in LVAD-bridged patients as we might have expected ($P < 0.001$).

Pulmonary artery circulation

An MPAP of ≥25 mm was present in 110 patients pre-operatively (110/158; 70%) and between 20 and 24 mmHg in 24 patients (24/158; 15%). The remaining 24 patients had an MPAP of <20 mmHg. The average MPAP across the entire cohort was 29 ± 10 mmHg, the PASP was 42 ± 14 mmHg, and the PADP was 21 ± 8 mmHg. In pre-operative cardiac transplant patients without LVAD, the average MPAP was 31 ± 10 mmHg, the PASP 44 ± 14 mmHg, and the PADP 22 ± 8 mmHg. Pulmonary arterial pressures were significantly lower in LVAD bridged patients (MPAP 26 ± 9 mmHg, $P = 0.04$; PASP 37 ± 14 mmHg, $P = 0.02$; and PADP 19 ± 7 mmHg, $P = 0.04$; *Table 2A*). No difference in pulmonary arterial pressures was observed according to natural history subtype (all $P > 0.05$, *Table 2B*).

Transpulmonary gradient (TPG) was 8.9 ± 4.0 mmHg across the entire cohort, 9.0 ± 4.2 mmHg in non-LVAD patients and 8.3 ± 3.5 mmHg in the LVAD group ($P = 0.63$; *Table 2A*). There was no significant difference in TPG according to natural history sub-type (all $P > 0.05$, *Table 2B*). Pulmonary vascular resistance (PVR) was 2.7 ± 2.0 WU across the cohort, 2.7 ± 1.6 WU in patients without LVAD, and 2.5 ± 2.9 WU in the LVAD-bridged patients. Although PVR was higher in patients without pre-operative LVAD, the difference was not statistically significant ($P = 0.39$; *Table 2A*). Pulmonary vascular resistance was higher in patients with a dilated cardiomyopathy and lower in those with valvular heart disease; however, neither relationship was found to be statistically significant ($P > 0.05$; *Table 2B*).

Ventricular function

Invasive haemodynamic indices of LV function were significant impaired in the study cohort as we might have expected. The mean CO was 3.9 ± 1.4 L/min, and CI was 2.1 ± 0.7 L/min. In pre-operative cardiac transplant patients without LVAD, the average CO was 3.7 ± 1.2 L/min, and CI was 2.0 ± 0.6 L/min. Cardiac output and CI were higher in LVAD patients owing to the mechanical circulatory support effect (CO 4.4 ± 1.7 L/min, $P = 0.13$; CI 2.3 ± 0.7 L/min, $P = 0.04$). Patients with valvular heart disease had higher CO and CI indices as we might have expected; however, neither value was statistically significant (both $P > 0.05$, *Table 2B*).

Table 1 Baseline demographic, clinical and echocardiographic data

	All ($n = 158$)	No-LVAD ($n = 115$)	LVAD ($n = 43$)	*P* value (No vs. LVAD)
Baseline demographics				
Age	48 ± 14	49 ± 13	48 ± 13	0.655
Gender (% female)	48 (31%)	35 (30%)	13 (30%)	$P < 0.001$
Dilated CM (%)		72 (63%)		
Ischaemic CM (%)		17 (15%)		
Infiltrative CM (%)		22 (19%)		
Valvular CM (%)		3 (3%)		
Other CM (%)		1 (<1%)		
Intra-operative considerations				
Transplant DIT (min)	220 ± 80	214 ± 84	226 ± 68	$P = 0.655$
Bypass time (min)	192 ± 57	183 ± 57	211 ± 59	$P = 0.180$
Redo median sternotomy	53 (35%)	21 (18%)	32 (74%)	$P < 0.001$
Concomitant valve surgery	2 (1%)	2 (2%)	0 (0%)	$P = 0.157$
Post-operative TTE				
RV base (mm)	32 ± 2	33 ± 2	32 ± 2	$P = 0.163$
PASP (mmHg)	29 ± 8	30 ± 10	27 ± 8	$P = 0.180$
TR burden prior to first biopsy				
Severe TR	12 (8%)	12 (10.4)	0 (0.0)	$P < 0.001$
Moderate TR	21 (13%)	15 (13.0)	6 (14.0)	$P = 1.00$
Post-operative clinical outcomes				
Post-op ECMO	33	27 (24%)	6 (14%)	$P < 0.001$
ICU LOS	11 ± 15	12 ± 17	13 ± 14	$P = 0.655$
Hospital LOS	33 ± 27	33 ± 29	32 ± 25	$P = 0.180$

Note: All values are mean ± standard deviation.
Abbreviations: DIT, donor ischaemic time; ECMO, extra corporeal membrane oxygenation; LOS, length of stay; PASP, pulmonary artery systolic pressure; RV, right ventricular; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram.

Table 2 (A) Intra-procedural right heart catheterization stratified by LVAD

	No-LVAD (n = 115)	LVAD (n = 43)	P value (No vs. LVAD)
RA (mmHg)	13.5 ± 6.6	11.2 ± 5.3	P = 0.06
PASP (mmHg)	43.6 ± 14.4	37.1 ± 13.6	P = 0.02
PADP (mmHg)	22.0 ± 8.1	18.9 ± 7.5	P = 0.04
MPAP (mmHg)	30.7 ± 9.8	26.4 ± 9.3	P = 0.04
CO (L/min)	3.7 ± 1.2	4.4 ± 1.7	P = 0.13
CI (L/min/m^2)	2.0 ± 0.6	2.3 ± 0.7	P = 0.04
TPG (mmHg)	9.0 ± 4.2	8.3 ± 3.5	P = 0.63
PVR (WU)	2.7 ± 1.6	2.5 ± 2.9	P = 0.39
PAPi	2.2 ± 2.0	2.3 ± 3.0	P = 0.97

Table 2 (B) Intra-procedural right heart catheterization stratified by natural history

	Dilated CM (n = 63)	Ischaemic CM (n = 17)	Infiltrative CM (n = 22)	Valvular CM (n = 3)	Other CM (n = 1)	P value (all pairwise comparisons)
RA (mmHg)	14.8 ± 7.0	13.3 ± 5.8	13.0 ± 4.7	19.0 ± 0.7	13.5 ± 6.6	All pairwise comparisons $P > 0.05$
PASP (mmHg)	43.2 ± 13.0	46.7 ± 15.1	40.3 ± 9.7	43.0 ± 8.4	43.6 ± 14.4	
PADP (mmHg)	23.4 ± 7.3	23.8 ± 7.3	19.7 ± 5.9	22.0 ± 4.9	22.0 ± 8.1	
MPAP (mmHg)	31.0 ± 8.7	30.2 ± 7.8	29.0 ± 7.0	30.0 ± 8.5	32.0 ± 7.0	
CO (L/min)	3.7 ± 1.1	3.7 ± 1.2	4.8 ± 1.0	5.3 ± 1.1	3.5 ± 1.2	
CI (L/min/m^2)	2.0 ± 0.5	2.0 ± 0.6	2.4 ± 0.5	2.8 ± 0.1	2.5 ± 0.5	
TPG (mmHg)	8.8 ± 3.9	9.1 ± 3.1	8.7 ± 4.7	9.5 ± 7.8	6.0 ± 3.2	
PVR (WU)	2.8 ± 1.5	2.7 ± 1.5	2.0 ± 1.7	1.7 ± 1.1	1.7 ± 1.4	
PAPi	1.9 ± 1.6	2.3 ± 1.5	1.9 ± 0.9	1.2 ± 0.3	1.1 ± 2.0	

Note: All values are mean ± standard deviation. (a) Pulmonary artery pressures were lower, and CI significantly higher in LVAD bridged patients ($P < 0.05$). (b) All pairwise comparisons according to underlying natural history were non-significant ($P > 0.05$).
Abbreviations: CI, cardiac index; CO, cardiac output; CM, cardiomyopathy; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PADP, pulmonary artery diastolic pressure; PAPI, pulmonary artery pulsatility index; PASP, pulmonary artery systolic pressure; TPG, transpulmonary gradient.

Systemic venous return

Right atrial pressure was considered as a surrogate measure of the systemic venous return. The mean RAP was 13 ± 6 mmHg across the entire study population. In patients without LVAD, the average RAP was 14 ± 7 mmHg. Although slightly lower, there was no significant difference in RAP when compared with patients bridged with LVAD (RAP 11 ± 5 mmHg, P = 0.06). No difference in RAP was observed according to natural history (all $P > 0.05$; *Table 2B*).

Pulmonary artery pulsatility index

The PAPi was derived as a surrogate measure of the entire right heart circulation. The average PAPi was 2.24 ± 2.29. This was 2.2 ± 2.0 in the pre-cardiac transplantation group without LVAD and 2.3 ± 3.0 in the pre-transplantation group with LVAD insertion (P = 0.97). The PAPi was higher in patients with an ischaemic cardiomyopathy (2.3 ± 1.5) and lower in those with valvular heart disease (1.2 ± 0.3; P = 0.180; *Table 2B*).

Correlation between PVR, PAPi, and other variables

Correlation between PAPi, PVR, TPG, and all-cause cardiovascular morbidity and mortality was assessed. Distribution of dilated, ischaemic, and infiltrative cardiomyopathies were significantly lower in the LVAD group (all $P < 0.05$); therefore, LVAD and natural history were analysed as separate categorical variables. Using a Mann–Whitney U test for comparison, there was no significant difference in the non-LVAD group in RA, PVR, or PAPi for mortality post-transplant (all $P > 0.05$). In the LVAD group, there was no significant difference in RA or PAPi for mortality outcomes (all $P > 0.05$); however, there was a significant difference in PVR between those that died post-transplant (2.8 ± 1.3 WU) and those still alive (1.8 ± 0.7 WU; P = 0.005) (*Table 3*). No mortality or ECMO events occurred in valvular heart disease or other cardiomyopathy patients (n = 0). The PAPi was non-significantly lower in the dilated cardiomyopathy group requiring ECMO post-operatively (P = 0.056); however, no significant association with mortality was demonstrated (*Table 3*).

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Table 3 Mann–Whitney *U* test for comparison of variables

	PAPi	TPG	PVR
ECMO			
LVAD	0.742	0.104	0.307
No-LVAD	0.971	0.412	0.868
Dilated CM	0.056	0.317	0.902
Ischaemic CM	0.610	0.332	0.447
Infiltrative CM	0.223	0.489	0.951
Mortality			
LVAD	0.187	0.065	0.005
No-LVAD	0.615	0.683	0.216
Dilated CM	0.299	0.563	0.789
Ischaemic CM	0.703	0.784	0.642
Infiltrative CM	0.739	0.693	0.847

Note: All values are mean ± standard deviation. No mortality or ECMO events occurred in patients with valvular or other CM (excluded from analysis). Raised PVR was associated with increased mortality in LVAD bridged patients ($P = 0.005$).
Abbreviations: CI, cardiac index; CO, cardiac output; CM, cardiomyopathy CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PADP, pulmonary artery diastolic pressure; PAPI, pulmonary artery pulsatility index; PASP, pulmonary artery systolic pressure; TPG, transpulmonary gradient.

Discussion

The findings of this study, the first to evaluate the prognostic impact of PAPi in cardiac transplant recipients, can be summarized as follows: Firstly, there was no association between PAPi and post-operative outcomes in patients who underwent cardiac transplantation; secondly, only PVR was associated with an increase in all-cause mortality and readmission for heart failure in cardiac transplantation patients bridged with an LVAD device. These findings suggest that the interpretation of PAPi is nuanced in reality, dependent on both the RV stroke volume and pulmonary artery capacitance, and thus, a single threshold cannot necessarily be applied to diverse patient populations such as cardiac transplant recipients.

Haemodynamic indices for prognostication of right heart failure

Increased pulmonary venous pressure secondary to left heart disease, or postcapillary PH, is the predominant cause of PH in patients with advanced heart failure. The diagnosis of PH due to left heart disease relies on a combination of MPAP and mean PAWP $\geq$20 mmHg and 15 mmHg, respectively. Postcapillary PH is associated with a decreased survival in proportion to increased pulmonary vascular gradients, decreased pulmonary arterial compliance, and reduced RV function. Isolated postcapillary pulmonary hypertension is generally associated with a TPG $\leq$ 12 mmHg, and a PVR $<$ 3 WU. A PVR $\geq$ 3 WU is consistent with combined pre- and post-capillary PH. Therefore, TPG and PVR are commonly used to differentiate heart failure patients with pulmonary vascular disease from those with post-capillary or passive PH. However, elevations in TPG and PVR may not always reflect precapillary PH.

Recently, it has been proposed that an elevated diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient (DPG) may be a better indicator of pulmonary vascular remodelling. In a large registry trial, elevated DPG was found to have no effect on post-transplant survival in patients with PH and an elevated TPG and PVR.[2] It was, however, associated with increased risk of RV failure but not mortality risk in patients post-LVAD insertion.[3] It is in this context that novel haemodynamic markers such as PAPi are increasingly being evaluated to better predict all-cause mortality and readmission for heart failure in cardiac transplantation patients.

Current clinical use of the PAPi

The PAPi was first described in patients with acute RV myocardial infarction in 2012 who were being considered for RVAD insertion.[4] As CO was largely determined by the RV assist device (RVAD) in these patients, the PAPi was thought to be a useful index for assessing RV recovery as it was not dependent on measurement of CO or stroke volume. The PAPi has more recently been evaluated in patients undergoing LVAD insertion to predict the risk of decompensated RHF post-operatively.[5,6] The mean PAPi in patients who developed RHF after LVAD ranged from 1.3 ± 0.5 to 1.7 ± 0.3 and subsequently a PAPi threshold of 1.85 was proposed. The PAPi has also been evaluated in patients with advanced heart failure.[7,8] A PAPi threshold of 3.65 had 83% sensitivity, 31% specificity and 71% positive predictive value for 6 month mortality and hospitalization in one study.[6,7]

PAPi as a prognostic indicator in patients undergoing cardiac transplantation

In patients undergoing heart transplantation, PAPi out-performed other indices to predict post-operative acute kidney injury which is associated with higher 1 year mortality.[9] To date, the prognostic value of PAPi in determining all-cause morbidity and mortality in heart failure patients undergoing cardiac transplantation has not been studied. Unlike its prognostic role in predicting acute kidney injury in heart transplant recipients, however, there was no correlation between the RAP, PA pressures or PAPi and post-operative mortality and heart failure hospitalization irrespective of bridging with a LVAD or underlying natural history. Only elevated PVR in LVAD-bridged patients was found to be predictive of mortality as we might have expected ($P = 0.005$).

Our findings highlight the complexities of the determinants that comprise the PAPi. Pulmonary artery pulse pressure (and systolic pressure) are dependent on both the RV stroke volume and the pulmonary arterial capacitance (PAC). That is, the PAPi may vary with changes in RV stroke volume, PAC, and RAP. The relationship between PAPi and RAP, for example, is non-linear, increasing rapidly at lower RAP with the increase being more marked at lower PAC,[10] all of which highlight the difficulties in uncoupling RV-PA interactions using this index. In the transplanted heart, where both the contractile function and systemic venous return are expected to normalize, the PAPi is not able to identify those with precapillary PH as accurately as PVR.

Study limitations

This is a retrospective registry study. The foremost limitation is the divergent nature of the non-LVAD and LVAD bridged cohorts. It is unlikely that a single PAPi threshold can be applied to our diverse heart failure population, as the same PAPi may be observed under very different loading conditions depending on state of compensation or decompensation, time prior to transplantation, and mechanical circulatory support. Our study is not large enough to allow propensity matched analysis, and thus, differences in the two populations confound whether it is the treatment or patient characteristics, which explain post-operative outcomes. Further longitudinal and prospective studies are needed to confirm and extend our results.

Conclusions

The PAPi has become widely accepted as a prognostic marker in patients with advanced heart failure, cardiogenic shock, and LVAD therapy. This index has multiple determinants and is able to reflect changes in any of the components of the right heart system—systemic venous system, RV function, and the pulmonary circulation. This study serves as a cautionary tale on the use of PAPi. Despite having a role in prognostication for RHF in PH and post-LVAD implantation, PAPi is not able to discriminate mortality outcomes for patients post-cardiac transplantation as it does not exclusively capture those with precapillary PH. Pulmonary vascular resistance, however, remains an important marker of mortality in an LVAD cohort bridged to transplant.

Perspectives

Owing to rapid advances in therapeutics and device technologies, it is of increasing physiological and clinical importance to understand and predict how the right ventricle may be affected by PH. Although the PAPi has become widely accepted as a prognostic marker in patients with advanced heart failure, cardiogenic shock, and LVAD therapy, PAPi is not able to discriminate mortality outcomes for patients post-cardiac transplantation as it does not exclusively capture those with precapillary pulmonary hypertension. Pulmonary vascular resistance, however, remains an important marker of mortality in an LVAD cohort bridged to transplant ($P = 0.005$).

Conflict of interest

All authors declare no conflict of interest.

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