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Determinants and prognostic implications of the negative diastolic pulmonary pressure gradient in patients with pulmonary hypertension due to left heart disease

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Aims The diastolic pressure gradient (DPG) has recently been introduced as a specific marker of combined pre-capillary pulmonary hypertension (Cpc-PH) in left heart disease (LHD). However, its diagnostic and prognostic superiority compared with traditional haemodynamic indices has been challenged lately. Current recommendations explicitly denote that in the normal heart, DPG values are greater than zero, with DPG ≥7 mmHg indicating Cpc-PH. However, clinicians are perplexed by the frequent observation of DPG <0 mmHg (DPG_{NEG}), as its physiological explanation and clinical impact are unclear to date. We hypothesized that large V-waves in the pulmonary artery wedge pressure (PAWP) curve yielding asymmetric pressure transmission might account for DPG_{NEG} and undertook this study to clarify the physiological and prognostic implications of DPG_{NEG}.

Methods and results Right heart catheterization and echocardiography were performed in 316 patients with LHD due to primary myocardial dysfunction or valvular disease. A total of 256 patients had PH-LHD, of whom 48% demonstrated DPG_{NEG}. The V-wave amplitude inversely correlated with DPG ($r = -0.45$, $P < 0.001$) in patients with low pulmonary vascular resistance (PVR), but not in those with elevated PVR ($P > 0.05$). Patients with large V-waves had negative and lower DPG than those without augmented V-waves ($P < 0.001$) despite similar PVR ($P > 0.05$). Positive, but normal DPG (0–6 mmHg) carried a worse 2-year prognosis for death and/or heart transplantation than DPG_{NEG} (hazard ratio 2.97; $P < 0.05$).

Conclusion Our results advocate against DPG_{NEG} constituting a measurement error. We propose that DPG_{NEG} can partially be ascribed to large V-waves and carries a better prognosis than DPG within the normal positive range.

Keywords Pre-capillary • Post-capillary • V-wave

Introduction

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD). In isolated post-capillary PH, the pulmonary arterial pressure (PAP) elevation is governed solely by the upstream-transmitted left atrial pressure (LAP). Long-standing post-capillary PH may, however, lead to pathological alterations of the pre-capillary vasculature, contributing to further PAP increase, a state denoted as combined post- and pre-capillary PH (Cpc-PH). Although this latter condition is clearly associated with worse prognosis,[1,2] the optimal method to distinguish these two cohorts haemodynamically remains controversial.

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Traditionally, pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG) have been employed for discerning Cpc-PH, both metrics bearing an established prognostic value in PH due to LHD (PH-LHD).[3,4] However, as both these markers are influenced by the LAP and stroke volume,[5] their specificity has been questioned. In recent times, the diastolic pulmonary gradient (DPG), considered less affected by heart failure- (HF) induced haemodynamic changes,[5] has been introduced as a more reliable Cpc-PH index. Based on the above rationale and study results demonstrating prognostic superiority of the DPG,[6,7] the Fifth World Symposium on PH proposed that a DPG ≥7 mmHg alone should define Cpc-PH.[5] However, the failure of two recent large-scale studies to confirm the prognostic value of DPG[8,9] raised concerns regarding its use in PH-LHD.[8,10] Despite the significant prevalence of a negative DPG values (DPG_{NEG}), reportedly varying between 10% and 50%,[8,11] the physiological background and the potential prognostic implications of DPG_{NEG} have not yet been investigated; rather, DPG_{NEG} has arbitrarily been considered to represent measurement error.[12] We hypothesized that prominent V-waves in the pulmonary artery wedge pressure (PAWP) recordings might account for the DPG_{NEG} by causing 'asymmetrical' pressure transmission through the pulmonary capillaries, i.e. a backward LAP wave reflection characterized by disproportionate phasic pressure changes. We therefore undertook the present study in order to (i) investigate the impact of V-waves on the DPG and particularly on the occurrence of DPG_{NEG}; (ii) elucidate the influence of PAWP as compared with direct LAP measurements on the DPG; and (iii) assess the prognostic significance of DPG_{NEG} compared with positive but normal DPG.

Methods

Study population

The study population consisted of 316 patients. A total of 192 patients were enrolled prospectively. 86 consecutive patients with PH due to heart failure (HF) (denoted as PH-LHD in the following) referred for right heart catheterization (RHC) for HF assessment between January and December 2014 were enrolled prospectively at Karolinska University Hospital, while 106 consecutive patients with severe rheumatic mitral valve stenosis (denoted as MS in the following) referred for percutaneous transvenous mitral commissurotomy (PTMC) between January and June 2012 were enrolled again prospectively at the Sri Sathya Sai Institute, Bangalore, India). In addition, 124 consecutive patients with PH-LHD referred for RHC at the Karolinska University Hospital were studied retrospectively. In all PH-LHD cases, medical treatment had been titrated and haemodynamic stabilization achieved at the time of examination. None of the patients included in the study presented with acute coronary syndrome or had undergone cardiac surgery within 1 year before enrolment. In the case of the MS cohort, subjects with >1 grade mitral regurgitation, aortic valve disease, ischaemic heart disease, AF, or hypertension were not included in the study. In the PH-LHD cohort, no specific exclusion criteria were applied, apart from the fact that patients with pressure tracings of inadequate quality (i.e. that would not have allowed reliable and reproducible identification of waveforms) were not included. A flowchart describing patient enrolment and haemodynamic grouping is provided in the supplementary material online, *Figure S1*. Follow-up data were collected form the Karolinska University Hospital database that is updated centrally; patients were followed until death, cardiac transplantation, or the end of the study period (mean time: 15.6 months). The prognostic value of DPG_{NEG} vs. positive but normal DPG was assessed. The study was approved by the local ethics committee (registration number 2013/1991-32). All prospectively enrolled subjects provided written informed consent. All subjects underwent transthoracic echocardiography and RHC.

Catheterization

Right heart catheterization was performed using a 6 F balloon-tipped fluid-filled Swan–Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) through jugular or femoral vein access. Mean right atrial pressure (RAP_M), diastolic (PAP_D), mean pulmonary artery pressure (PAP_M), mean pulmonary artery wedge pressure ($PAWP_M$), and right ventricular systolic pressure (RVSP) was recorded under fluoroscopy after calibration with the zero level set at the mid-thoracic line. All pressure tracings were stored in a connected haemodynamic recorder and analysed offline with commercially available software (Xper Information Management, Philips Medical Systems, The Netherlands). Importantly, in order to ensure the uniformity of data acquisition and the standardization of the study, the same investigator (A.M.) participated in RHC for all MS and the majority of PH-LHD patients and performed the analysis of all waveforms at both sites. From the PAWP recordings, the peak V- and A-wave and the $PAWP_M$ were obtained. All pressure measurements were averaged from a minimum of five heart cycles at end-expiration. Cardiac output (CO) was measured using Fick's principle. The oxygen consumption was measured breath by breath by a dedicated gas analysis system. In 15 cases, thermodilution was employed.

The PVR, TPG, and DPG were calculated as: $PVR = (PAP_M - PAWP_M)/CO$; $TPG = PAP_M - PAWP_M$; and $DPG = PAP_D - PAWP_M$, respectively. The difference between TPG and DPG (ΔPG), which equals $PAP_M - PAP_D$, was analysed in order to investigate diagnostic discrepancies by the two measures. The right ventricular stroke work index was calculated as $RVSWi = (PAP_M - RAP_M) \times SVi \times 0.0136$, where SVi denotes the stroke volume index measured as: CO/heart rate (HR)/body surface area (BSA). In MS patients, measurements were performed prior to PTMC. For full details of methods, please see the supplementary material online.

Simultaneous left atrial pressure and pulmonary artery wedge pressure assessment

In 51 MS patients, simultaneous, beat-to-beat, LAP and PAWP tracings were obtained concurrently with RHC. Interatrial septal puncture was performed with an 8 F Mullins' sheath, dilator and a Brockenbrough needle. The LAP was measured directly through the Mullins' sheath used during valvuloplasty. Both transducers were zeroed after careful calibration, pressures were recorded during a 10 sec period and stored for offline analysis.

Statistical analysis

The IBM SPSS statistics version 23.0 was used. Normality was tested by the Kolmogorov–Smirnov test. Continuous variables were

expressed as mean ± SD or median and interquartile range. Categorical variables were expressed as absolute values and percentage. Comparisons of groups were performed with Mann–Whitney rank-sum test. Correlations were tested by the Pearson's two-tailed test. All tests were performed at 95% confidence intervals (CIs). A *P*-value of <0.05 was considered statistically significant. Receiver operator characteristic (ROC) curve analysis was performed. Survival was analysed in the retrospectively studied 124 PH-LHD patients with Kaplan and Meier non-parametric test and compared using a log-rank test. Univariate and multiple Cox proportional hazards regression models were used to examine the effects of the DPG on patients' survival. Age-, creatinine-, and sex-adjusted survival curve estimates of the DPG were derived from stratified Cox models.

Results

Study population

Of the 316 patients enrolled, 269 (84.5%) demonstrated PH (PAP_M ≥25 mmHg). Of these, 256 (MS: 37%) had PH-LHD (PAP_M ≥25 mmHg and $PAWP_M$ > 15 mmHg). Demographics are presented in *Table 1*. Due to the different underlying pathology, the MS and PH-LHD groups were analysed separately. MS patients had higher PAP_M, A- and V-waves, and RVSWi compared with the PH-LHD group. However, DPG did not differ between the two groups (*Table 2*).

V-wave influence on the diastolic pulmonary pressure gradient

To evaluate the effect of the V-waves on the DPG, we subgrouped the cohort based on the presence of large V-waves, defined as the V-wave exceeding the $PAWP_M$ by the arbitrary limit of >10 mmHg as previous investigators have performed.[13] In the 69 cases (45%) with large V-waves (43 MS and 26 PH-LHD patients), the DPG was on average negative and lower ($P < 0.05$) compared with those with smaller V-waves, despite similar levels of TPG, PVR, PAP, and cardiac index ($P > 0.05$, for all comparisons; *Table 3*; Supplementary material online, *Figure S2*).

A significant inverse correlation between the V-wave and DPG was evident in patients with PVR <3 Wood Units (WU) ($r = -0.45$, $P < 0.001$), both in the MS ($r - 0.34$, $P = 0.03$) and in the PH-LHD group ($r = -0.46$, $P < 0.001$). A weaker, yet statistically significant inverse correlation ($r = -0.36$; $P = 0.01$) between the V-wave and DPG was found in patients with a PVR of 3–7 WU. However, this relationship disappeared at higher PVR values ($P > 0.05$; *Figure 1A*). Conversely, no association between the V-wave and TPG was observed ($P > 0.05$; *Figure 1B*). The modest overall correlation between the V-wave and DPG might be ascribed to the divergent association of the V-waves with PAP_D at higher PAP_M and PVR (*Figure 1D*), whereas the association between V-waves and $PAWP_M$ was essentially unaltered throughout the examined PAP_M and PVR range (*Figure 1C*).

Importantly, in patients with PVR <3 WU, the V-wave showed the strongest correlation with the ΔPG ($r = 0.45$, $P < 0.001$ for the whole cohort, $r = 0.36$, $P = 0.005$ for PH-LHD; $r = 0.6$, $P = 0.003$ for the MS group, *Figure 1E*), with a weaker yet significant association of both the absolute and relative V-wave value with ΔPG ($r = 0.26$ and $r = 0.19$, respectively; $P < 0.05$). Conversely, neither the A-wave nor the CO correlated with ΔPG ($P > 0.05$, in all cases).

The puzzling finding of normal DPG with concomitantly elevated TPG (>12 mmHg) is not unusual. Indeed, in our study 59 patients (23%, MS: 29%), TPG and DPG demonstrated incongruent diagnostics (TPG >12 mmHg, DPG <7 mmHg). Furthermore, DPG_{NEG} with concomitantly elevated TPG (>12 mmHg) occasionally occurs. In our study, we decided to quantify this discrepancy by calculating ΔPG (ΔPG = TPG – DPG). The ΔPG value that leads to discrepant Cpc-PH diagnostics between TPG and DPG_{NEG} is 12 mmHg. In order to examine whether the V-wave amplitude impacted on this discrepancy, we employed ROC analysis in patients with PVR <3 WU. The association between ΔPG and V-wave amplitude is presented in *Figure 1E*. At an optimal cut-off limit of 30.5 mmHg, V-wave yielded a sensitivity of 85% and specificity of 70% [area under the curve (AUC) 0.80, 95% CI 0.72–0.88; $P < 0.001$) for the identification of ΔPG >12 mmHg (Supplementary material online, *Figure S3*). For the whole cohort of patients with PVR <7 WU, the corresponding figures were: AUC 0.73, $P < 0.003$; 95% CI 0.61–0.84 at an optimal cut-off limit of V-wave of 31.5 mmHg.

In an attempt to investigate potential non-invasive and clinical determinants of the V-wave amplitude, left atrial end-systolic volume index (LA-ESVi), LV mass index (LVMi), internal LV dimensions, as well as the available clinical variables were tested. None of the tested variables, however, was associated with the V-wave ($P > 0.05$ in all cases).

Negative diastolic pulmonary pressure gradient values

In total, 123 patients (48%) demonstrated DPG_{NEG} (median −3 mmHg; interquartile range −5 to −2 mmHg) with higher prevalence in the MS compared with the PH-LHD group (55% vs. 44%, $P < 0.05$). MS patients had significantly higher V-waves ($P < 0.001$, *Table 2*). When the whole study population was considered, patients with DPG_{NEG} showed significantly larger V-waves and lower PAP_M, RAP_M, PVR, and TPG values, whereas the $PAWP_M$ and cardiac index levels were comparable with those with positive DPG (*Table 4*).

Assuming that pre-capillary changes differ between positive DPG and DPG_{NEG} patients, we compared the two groups within a pre-defined PVR range (3–7 WU) in order to ensure a comparatively equivalent degree of pre-capillary alterations between the two groups. Patients with DPG_{NEG} demonstrated higher V-waves in both the MS and PH-LHD group, and a less prominent right heart dilatation along with better RV function ($P < 0.001$) as compared with the positive DPG cohort, despite similar PAP_M ($P > 0.05$, *Table 4*; Supplementary material online, *Table S1*). Interestingly, the V-wave amplitude was similar in MS and PH-LHD patients in the DPG_{NEG} group.

Table 1 Demographic and echocardiographic data of the study population.

	All patients (256)	MS (94)	PH-LHD (162)	*P*-value	PH-LHD R (124)
Demographics					
Age	50 ± 19	31 ± 9	61 ± 15	<0.001	61 ± 15
Female (%)	51%	72%	39%	<0.001	40%
BSA (m^2)	1.8 ± 0.3	1.4 ± 0.2	2.0 ± 0.2	<0.001	1.9 ± 0.2
HT (%)		0%	85%		51%
DM (%)		0%	60%		45%
Aetiology of HF					
IHD (*n*, %)		0%	36 (22%)		32 (26%)
Idiopathic HF			68 (42%)		48 (39%)
Myocarditis			21 (13%)		6 (5%)
Other			37 (23%)		38 (31)
AF (*n*, %)	53 (21%)	0	53 (33%)		43 (35%)
Functional class					
NYHA II – IIIa		60 (64%)	84 (52%)	<0.001	70 (56%)
NYHA IIIb		34 (36%)	49 (30%)	<0.001	29 (23%)
NYHA IV		–	29 (18%)		25 (20%)
Medication					
Diuretics		100%	81%		78%
ACE inhibitor			85%		81%
Beta-blocker		100%	98%		93%
CCA			25%		18%
MRA			31%		34%
Echo data					
EF ≤45%					
	69 (27%)	5 (5%)	62 (38%)	<0.001	55 (44%)
LVEDD (mm)		44 ± 7	52 ± 13	<0.001	54 ± 14
LVESD (mm)		29 ± 0.4	41 ± 15	<0.001	43 ± 16
LVMi (g/m^2)		64 ± 18	105 ± 50	<0.001	114 ± 55
LA-ESVi (mL/m^2)		68 ± 19	50 ± 21	<0.001	58 ± 20
MVA (cm^2)		0.8 ± 0.2			
MVG (mmHg)		19 ± 9			
RVEDD (mm)		36 ± 5	40 ± 8	<0.001	41 ± 7
TAPSE (mm)		18 ± 3	14 ± 5	<0.001	14 ± 4
MR grade					
Mild	163 (63%)	64 (68%)	99 (61%)	<0.001	82 (66%)
Moderate	23 (9%)	–	23 (14%)		14 (11%)
Severe	17 (6%)	–	17 (10.5%)		11 (9%)
AS grade					
Moderate	3 (1%)	–	3 (2%)		4 (3%)
AR (grade)					
Mild	32 (13%)	–	32 (20%)		31 (25%)
Moderate	3 (1%)	–	3 (2%)		6 (5%)

Data are expressed as expressed as mean ± SD.
P-values indicate the difference between the two prospective cohorts, i.e. MS and LHD.
AR, aortic valve regurgitation; AS, aortic valve stenosis; BSA, body surface area; CCA, calcium channel blocker; DM, diabetes mellitus; HR, heart rate; IHD, ischaemic heart disease; MS, mitral valve stenosis; PH-LHD, pulmonary hypertension due to myocardial dysfunction; PH-LHD R, retrospective arm of the PH-LHD group; HT, hypertension; LA-ESVi, left atrial end-systolic volume index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVMi, LV mass index; MRA, mineralocorticoid receptor antagonist; MVA, mitral valve area; MVG, mitral valve mean diastolic gradient; RVEDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular positive systolic excursion; MR, mitral valve regurgitation.

Determinants of the diastolic pulmonary pressure gradient

Left atrial pressure vs. pulmonary artery wedge pressure in diastolic pulmonary pressure gradient assessment

In the 51 MS patients with simultaneous PAWP and LAP recordings, the DPG was calculated from PAWP (DPG_{PAWP}) and LAP (DPG_{LAP}) separately. DPG_{PAWP} was negative in 28 cases while DPG_{LAP} was negative in 22 cases, due to a slightly yet not significantly lower (mean bias: – 2 mmHg) LAP (24.1 ± 8.0 mmHg) as compared with PAWP (26.0 ± 8.1 mmHg; $P > 0.05$). However, in only three cases with negative DPG_{PAWP} was the corresponding DPG_{LAP} positive, while in one case reclassification occurred in the opposite direction.

Table 2 Haemodynamics of the entire cohort

	All patients (256)	MS (94)	PH-LHD (162)	*P*-value
PAP_M (mmHg)	35 (29 to 44) (256)	38 (30 to 50) (94)	34 (29 to 43) (162)	0.024
PAP_D (mmHg)	24 (20 to 31) (255)	27 (19 to 36) (94)	23 (20 to 29) (161)	0.026
RVSP (mmHg)	24 (21 to 29) (256)	59 (47 to 83) (94)	40 (49 to 63) (162)	<0.001
$PAWP_M$ (mmHg)	24 (21 to 29) (256)	25 (23 to 32) (94)	23 (20 to 27) (162)	0.026
A-wave (mmHg)	26 (22 to 32) (229)	31 (26 to 37) (91)	24 (21 to 28) (138)	<0.001
V-wave (mmHg)	31 (27 to 37) (235)	35 (31 to 44) (94)	28 (25 to 33) (141)	<0.001
CI (L/min/m^2)	1.9 (1.6 to 2.4) (256)	1.7 (1.4 to 2.1) (94)	2 (1.7 to 2.5) (162)	<0.001
RAP_M (mmHg)	10 (6 to 15) (255)	6 (3.8 to 8) (94)	12 (9 to 17) (161)	<0.001
RVSWi (g/m^2/beat)	9 (6.6 to 13) (255)	10.4 (7.8 to 14.8) (94)	8.2 (6 to 12.2) (161)	<0.001
AV (mL/L)	54 (45 to 65) (241)	50 (42 to 57) (94)	57 (45 to 17) (147)	<0.001
DPG (mmHg)	0 (−3 to 4) (255)	−1 (−4 to 5) (94)	0 (−3 to 3) (161)	0.327
DPG <7	−1 (−4 to 1) (83%)	−2 (−5 to 0) (79%)	−1 (−3 to 1) (85%)	
DPG ≥7	13 (9 to 15) (17%)	14 (10 to 18) (21%)	12 (9 to 14) (14%)	
TPG (mmHg)	10 (7 to 18) (256)	9 (6 to 21) (94)	11 (7 to 16) (162)	0.72
TPG ≤12	8 (5.5 to 9) (61%)	7 (5 to 9) (62%)	8 (6 to 10) (61%)	
TPG >12	20 (16 to 27) (39%)	25 (18 to 34) (38%)	19 (15 to 23) (39%)	
PVR (WU)	3 (1.8 to 5.2) (256)	4 (2.5 to 8.8) (94)	2.6 (1.7 to 4.5) (162)	<0.001
PVR <3	1.8 (1.4 to 2.5) (51%)	1.9 (1.3 to 2.6) (36%)	1.8 (1. 3 to 2.4) (59%)	
PVR ≥3	5.3 (3.8 to 7.8) (49%)	7.1 (4.1 to 11.6) (64%)	4.8 (3.8 to 6.1) (41%)	

Values are expressed as the median and interquartile range.
P-values report the statistical difference between MS and LHD.
AV, arteriovenous difference of oxygen saturation; CI, cardiac index; DPG, diastolic pulmonary pressure gradient; MS, mitral stenosis; PAP_M, PAP_D, pulmonary artery mean and diastolic pressure, respectively; $PAWP_M$, mean pulmonary artery wedge pressure; PH-LHD, pulmonary hypertension due to myocardial dysfunction; PVR, pulmonary vascular resistance; RAP_M, mean right atrial pressure; RVSP, right ventricular systolic pressure; RVSWi, right ventricular stroke work index; TPG, transpulmonary pressure gradient; V- and A-wave, the maximal amplitude of the V- and A-wave of the PAWP waveform, respectively; WU, Wood Units.

Table 3 Haemodynamics stratified according to V-wave amplitude

	Small V-waves *n* = 166 (51 MS)	Large V-waves *n* = 69 (43 MS)	*P*-value
PAP_M (mmHg)	34 (29 to 44)	35 (30 to 45)	0.36
PAP_D (mmHg)	24 (20 to 30)	23 (19 to 32)	0.77
$PAWP_M$ (mm Hg)	23 (20 to 27)	25 (22 to 31)	0.001
V-wave (mmHg)	28 (25 to 32)	39 (34 to 46)	<0.001
$V\text{-wave}_{abs}$ (mmHg)	5 (3 to 7)	13 (11 to 17)	<0.001
PVR (WU)	2.9 (1.9 to 5.6)	3.1 (1.7 to 5.2)	0.73
TPG (mmHg)	11 (7 to 19)	9 (7 to 15)	0.39
DPG (mmHg)	0 (−2 to 5)	−2 (−4 to 1)	0.002
CI (L/min/m^2)	1.9 (1.6 to 2.4)	1.8 (1.6 to 2.5)	0.26

Values are expressed in median and interquartile range.
Small V-wave signifies a difference between maximal amplitude of the V-wave of the PAWP waveform (PAWPv) and the mean pulmonary artery wedge pressure ($PAWP_M$), i.e. $V\text{-wave}_{abs}$ of <10 mmHg.
Large V-wave signifies a $V\text{-wave}_{abs}$ ≥10 mmHg.
CI, cardiac index; DPG, diastolic pulmonary pressure gradient; MS, mitral stenosis; PAP_M and PAP_D, pulmonary artery mean and diastolic pressure, respectively; $PAWP_M$, mean pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary pressure gradient; WU, Wood Units.

Heart rhythm

When the analysis was confined to the 192 patients with HR < 85 b.p.m., 52% demonstrated DPG_{NEG}. Similarly, when only the 53 patients in AF were considered, DPG_{NEG} was measured in 50%.

Alternative pulmonary artery wedge pressure measurements

As detailed in the Supplementary Results online, when the DPG was calculated using the PAWP value measured at the z-point of the PAWP curve, instead of using $PAWP_M$ in patients with DPG_{NEG}, this resulted in significantly higher DPG values. Still, the prevalence of DPG_{NEG} was not significantly reduced.

Prognostic value of the diastolic pulmonary pressure gradient

Two-year outcome for the combined endpoint of death or cardiac transplantation was significantly better for PH-LHD patients with

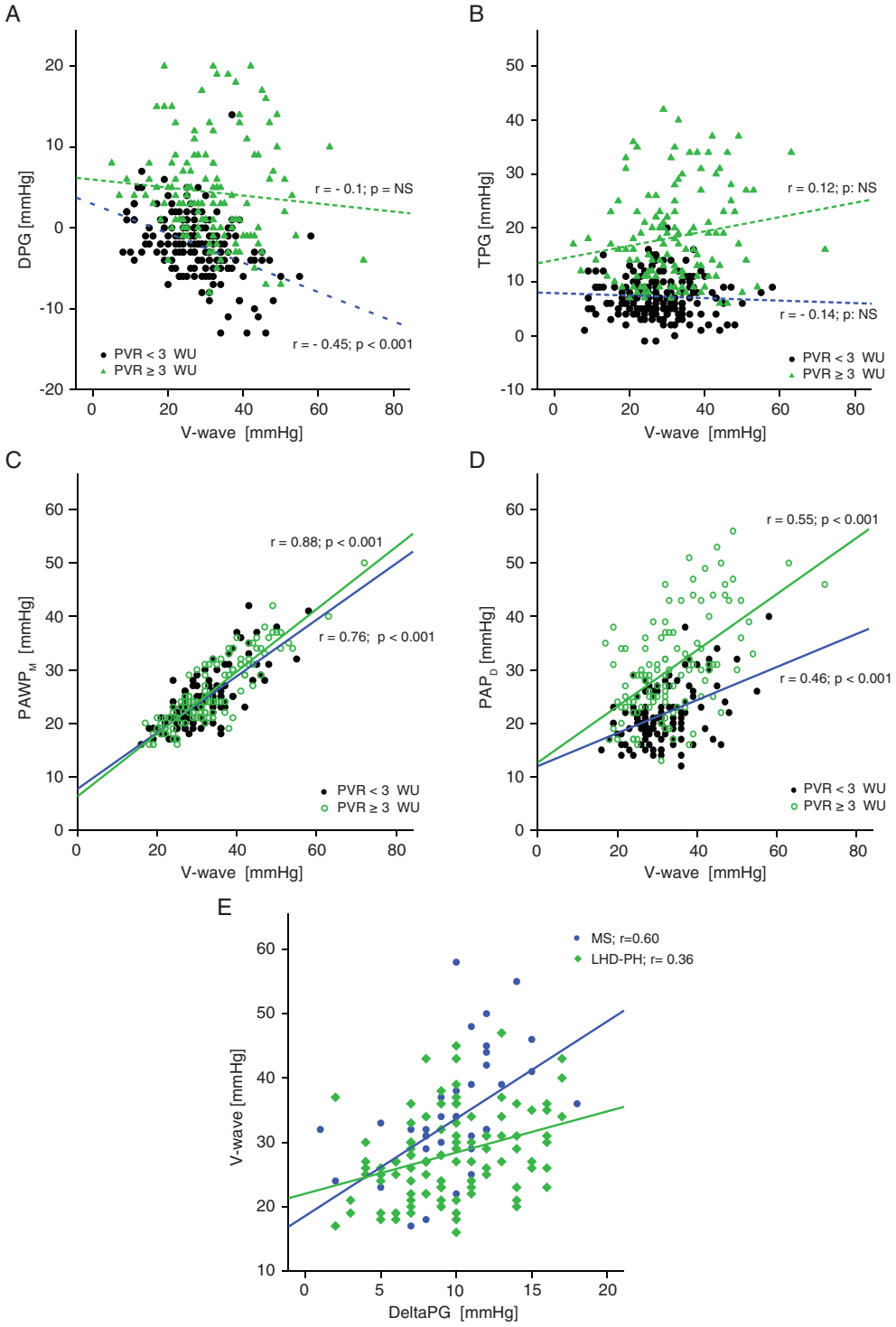


Figure 1 (*A*) Correlation between the diastolic pulmonary pressure gradient (DPG) and the V-wave amplitude in patients with low (PVR <3 WU) and high (PVR ≥ 3 WU) pulmonary vascular resistance. (*B*) Correlation between the transpulmonary pressure gradient (TPG) and the V-wave amplitude in patients with low (PVR <3 WU) and high (PVR ≥3 WU) PVR. (*C*) Correlation between the mean pulmonary artery wedge pressure ($PAWP_M$) and the V-wave amplitude in patients with low (PVR <3 WU) and high (PVR ≥3 WU) PVR. (*D*) Correlation between the diastolic pulmonary artery pressure (PAP_D) and the V-wave amplitude in patients with low (PVR <3 WU) and high (PVR ≥3 WU) PVR. (*E*) Correlation between the V-wave amplitude and ΔPG in patients with MS (mitral valve stenosis) and PH-LHD (pulmonary hypertension due to left heart disease). WU, Wood Units.

Table 4 Comparison of negative and positive diastolic pulmonary pressure gradient groups within the entire study population and in patients with a predefined pulmonary vascular resistance range of 3–7 Wood Units

	All patients		PVR 3–7 WU	
	DPG <0 (*n*)	DPG ≥0 (*n*)	DPG <0 (*n*)	DPG ≥0 (*n*)
MS patients (*n*)	52 (42 %)	42 (32 %)	18 (64 %)	11 (19 %)
PAP_M (mmHg)	31 (28 to 37) (123)	41 (33 to 49) (132) ($P<0.001$)	38 (30 to 43) (28)	40 (34 to 45) (57) ($P=0.128$)
PAP_D (mmHg)	20 (17 to 26) (123)	28 (23 to 35) (132) ($P<0.001$)	23 (18 to 30) (28)	27 (24 to 31) (57) ($P=0.013$)
V-wave (mmHg)	33 (28 to 39) (112)	29 (25 to 36) (123) ($P<0.001$)	37 (32 to 42) (26)	28 (24 to 33) (52) ($P<0.001$)
$PAWP_M$ (mmHg)	24 (21 to 29) (123)	24 (20 to 28) (132) ($P=0.06$)	25 (21 to 32) (28)	24 (20 to 28) (57) ($P=0.071$)
RVSP (mmHg)	49 (41 to 59) (123)	62 (47 to 78) (132) ($P<0.001$)	51 (46 to 32) (28)	61(47 to 71) (56) ($P=0.67$)
RAP_M (mmHg)	9 (5 to 13.5) (123)	11 (7 to 15) (132) ($P=0.004$)	7.5 (4 to 10) (28)	11 (7 to 15) (57) ($P=0.005$)
PVR (WU)	2.2 (1.4 to 3.0) (123)	4.7 (2.6 to 7.6) (132) ($P<0.001$)	4 (3.4 to 4.8) (28)	4.7 (3.7 to 5.6) (57) ($P=0.09$)
DPG (mmHg)	−3 (−5 to −2) (123)	3 (1 to 9) (132) ($P<0.001$)	−2.5 (−4 to −1) (28)	3.0 (1 to 5) (57) ($P<0.001$)
TPG (mmHg)	7 (5 to 9) (123)	16 (11 to 24) (132) ($P<0.001$)	9 (8 to 14) (28)	15 (12 to 21) (57) ($P<0.001$)
CI (L/min/m^2)	1.9 (1.6 to 2.5) (123)	1.9 (1.6 to 2.3) (132) ($P=0.392$)	1.7 (1.3 to 1.9) (28)	1.8 (1.6 to 2.2) (57) ($P=0.034$)
RVSWi (g/m^2/beat)	8.2 (6.4 to 11) (123)	10.5 (6.8 to 15) ($P=0.004$)	8.4 (6 to 12.6) (28)	10.3 (6.3 to 14) (57) ($P=0.24$)
A–V (mL/L)	49 (42 to 59) (115)	58 (48 to 69 (126) ($P<0.001$)	49 (41 to 63) (28)	62 (49 to 71) (53) ($P=0.04$)
TAPSE (mm)	17 (12 to 19) (123)	15 (12 to 18) (132) ($P=0.025$)	18 (15 to 21) (28)	14 (11 to 17) (57) ($P=0.004$)
RA area (cm^2)	18 (12 to 24) (123)	22 (15 to 27) (132) ($P=0.002$)	12 (10 to 24) (28)	23 (18 to 29) (57) ($P<0.001$)
RVEDD (mm)	36 (33 to 41) (123)	38 (34 to 46) (132) ($P<0.003$)	34 (33 to 43) (28)	40 (36 to 48) (57) ($P=0.005$)

Values are expressed ad the median and interquartile range.
A–V, arteriovenous difference in oxygen saturation; CI, cardiac index; DPG, pulmonary diastolic pressure gradient; MS, mitral stenosis; PAP_M and PAP_D pulmonary artery mean and diastolic pressure, respectively; $PAWP_M$ and V-wave, mean pulmonary artery wedge pressure and the maximal amplitude of the V-wave of the PAWP waveform, respectively; PVR, pulmonary vascular resistance; RA, right atrial; RAP_M, right atrial mean pressure; RVEDD, right ventricular end-diastolic diameter; RVSP; right ventricular systolic pressure; RVSWi, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary pressure gradient; WU, Wood Units.

DPG_{NEG} as compared with those with positive but normal DPG ($0 \leq$ DPG <7 mmHg) (*Figure 2A*). In the DPG_{NEG} group ($n=57$), the combined endpoint was documented in 16 cases (10 deaths and 6 transplantations), while in the $0 \leq$ DPG <7 mmHg group ($n=53$) the corresponding figures were 24 (14 deaths and 10 transplantations). Finally, in the DPG ≥7 mmHg group ($n=17$), eight combined endpoint events were recorded (5 deaths and 3 transplantations).

The occurrence of the combined endpoint of death or transplantation was significantly higher for $0 \leq$ DPG <7 mmHg both in unadjusted analysis ($P<0.005$) and when adjusted for age, creatinine, and ischaemic heart disease (*Figure 2B*). Conversely, neither TPG (cut-off 12 mmHg) nor PVR (cut-off 3 WU) provided significant prognostic information ($P=0.522$ and $P=0.718$, respectively). Furthermore, combining DPG and TPG (DPG_{NEG} and TPG ≤12 mmHg vs. $0 \leq$ DPG <7 mmHg and TPG >12 mmHg) also failed to provide prognostic information ($P=0.223$).

Discussion

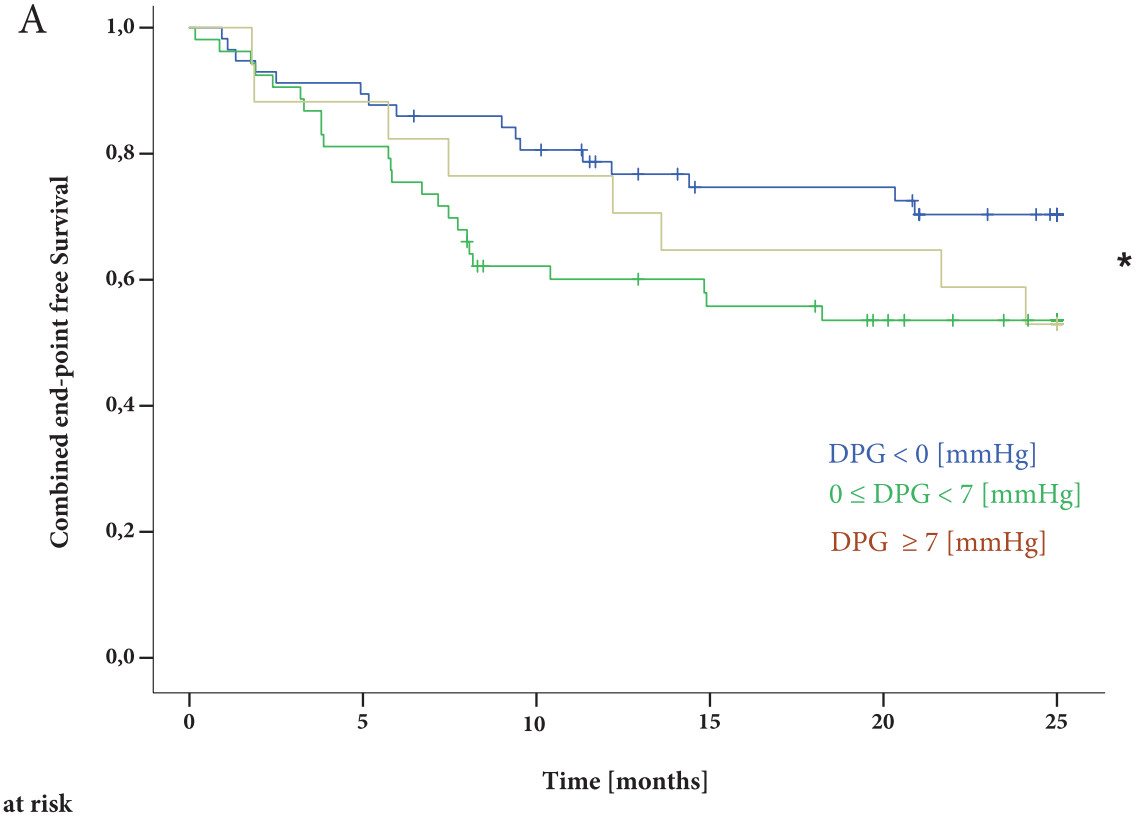
In the present study, we (i) confirm the high prevalence of DPG_{NEG} in PH-LHD patients; (ii) demonstrate that DPG_{NEG} does not always represent measurement error, but instead may be ascribed to high V-wave amplitude in patients with relatively low resistance in the pulmonary vascular bed; and (iii) show that DPG_{NEG} is associated with lower mortality as compared with the corresponding group of positive yet not elevated DPG.

In healthy subjects and in patients without significant pre-capillary alterations, PAP_D is closely related to the LAP, with DPG values ranging between 0 and 5 mmHg.[5] DPG_{NEG} values have so far been regarded as measurement bias, ascribed to overwedging or inaccurate PAP_D recordings.[5] However, the high DPG_{NEG} prevalence, ranging from 20% in critically ill patients[11,14] to 35%[8] and up to 50%[15] in PH-LHD patients, calls for a reappraisal of its pathophysiological origin. DPG_{NEG} was found in 44% of our PH-LHD cohort, most probably reflecting the higher proportion of PH (95%) compared with that (45%) in a recent study.[8]

The V-wave influence on the diastolic pulmonary pressure gradient

During systole, the second phase of LA filling occurs, yielding the most prominent positive deflection of the PAWP waveform designated as the V-wave. The volume and the rate of blood entering the left atrium as well as this chamber's compliance determine the V-wave's amplitude,[16,17] which in healthy subjects averages 12 mmHg, ranging between 4 and 19 mmHg, being at most 6 mmHg higher than the LAP_M.[18] Importantly, the LA volume–pressure relationship follows an exponential rather than a linear pattern, so that at lower LAP a certain volume entering the left atrium yields minor pressure elevation, whereas at higher LAP an equal inflowing volume results in a greater pressure rise.[13,16] Conceivably, large V-waves arise not only in the presence of severe acute mitral regurgitation[19] but also in conditions such as MS[20] and long-standing LV dysfunction, when LA distensibility is impaired, resulting in an upward shift of the LA volume–pressure curve. In our

A



Number at risk

DPG < 0 [mmHg]	57	51	45	35	35	26
0 ≤ DPG < 7 [mmHg]	53	43	30	26	22	17
DPG ≥ 7 [mmHg]	17	15	13	11	11	8

B

DPG [cutoff = 0 mm Hg]	Hazard ratio for death and /or HTX	95% CI	P-value
Unadjusted	2.44	1.02 - 5.81	0.04
Adjusted for Age	2.85	1.15 - 7.08	0.02
Adjusted for Creatinine	2.58	1.07 - 6.23	0.03
Adjusted for IHD	2.76	1.14 - 6.66	0.02
Adjsuted for All above	2.97	1.21 - 7.31	0.01

Figure 2 (*A*) Kaplan–Meier analysis for the three diastolic pulmonary pressure gradient (DPG) groups. Group I, DPG <0 mmHg; Group II, 0 ≥ DPG <7 mmHg; Group III, DPG ≥7 mmHg. (*B*) Hazard ratio for death and/or transplantation for patients with positive normal DPG (0 ≤ DPG <7 mmHg) and negative DPG. Due to few patients in Group III, only the statistical comparison between Group I and II is presented. CI, confidence interval; HTX, heart transplantation; IHD, ischaemic heart disease.

study, large V-waves were present in 20% of the PH-LHD group and in 46% of the MS cohort, similar to the findings of Wang and colleagues.[20] It should be emphasized that the augmented V-waves in these two cohorts represent distinct haemodynamic conditions; in MS it reflects increased LA stiffness due to obstructed mitral valve orifice, whereas in PH-LHD it is mainly secondary to a rise in LV end-diastolic pressure (LVEDP). It has been shown that the distorted LAP waveform in the presence of large V-waves leads to overestimation of the LVEDP.[21] Furthermore, there is evidence of retrograde superimposition of prominent V-waves on the PAP contour.[22] Caro and colleagues demonstrated that at high LAP, the ratio of pulmonary arterial to pulmonary venous compliance changes, promoting an asymmetrical backward transmission of the phasic LAP.[23] Although studies concomitantly reporting the V-wave amplitude and the PAP_D are infrequent, the existing data on large V-waves in the context of increased LA stiffness reveal DPG_{NEG} in essentially all cases.[17] Importantly, we demonstrate that the inverse correlation between the V-wave and DPG was confined to patients with relatively low PVR, in accordance with the findings of Falicov and colleagues.[15] Under physiological conditions, at end-diastole, the pulmonary vascular bed allows pressure equilibration[24] which is otherwise hindered by the presence of vascular remodelling. Taken together, our results indicate that in PH-LHD the V-wave amplitude significantly influences the DPG calculation unless significant pre-capillary remodelling is present. However, with progressive maladaptive pre-capillary alterations, the V-wave no longer acts as an important determinant of the DPG, which might be explained by increased stiffening of the pulmonary arteries and thus dampening of the backward LAP transmission. Previous investigations suggest that large V-waves inversely correlate to the ratio between the systolic and diastolic pulmonary inflow velocities.[25] In accordance with previous investigators, LA volume was not associated with the V-wave amplitude.[26] As echocardiography plays a key role in the initial PH assessment in HF, further studies are warranted to address potential incremental value of this modality.

Methodological considerations

The current findings argue against the notion that DPG_{NEG} represents merely inaccurate measurement. First, the PAWP and PAP waveforms were assessed manually at end-expiration by a single investigator, limiting the possibility of erroneous computerized PAP_D measurements and preventing potential $PAWP_M$ underestimation due to pressure averaging throughout the respiratory cycle.[27] Experimental studies have shown that HR impacts on DPG; at higher HR, DPG rises due to lower LVEDP and a concomitant PAP_D elevation.[28] Our results reveal that even when confining the analysis to patients with normal HR or patients with AF, the incidence of DPG_{NEG} was unaltered. Finally, our simultaneously performed PAWP and LAP measurements partly contradict the opinion that DPG would be a result of erroneous PAWP recordings. Direct LAP measurements yielded slightly higher DPG values as compared with PAWP. In ~11% cases with negative DPG_{PAWP}, the corresponding DPG_{LAP} was positive, while in one case reclassification occurred in the opposite direction (4.5%). This finding points to the fact that due to its low absolute value, even a small measurement error will affect the DPG value; however, it also demonstrates that measurement error accounts for only a minority of DPG_{NEG} cases. Taken together, although the slight discrepancy between LAP and PAWP might account for a minor portion of the DPG_{NEG}, our findings suggest that DPG_{NEG} values can for the most part be ascribed to the augmented V-waves.

Prognostic significance

The prognostic impact of DPG_{NEG} is as yet unknown. It has been suggested that patients with DPG_{NEG}, instead of being a subclass of the isolated post-capillary PH (DPG <7 mmHg) group, in fact represent a cohort with worse haemodynamics.[8] Our findings contradict this hypothesis. We demonstrate that when comparing DPG_{NEG} patients with those with $0 \leq$ DPG <7 mmHg, within a pre-defined range of PVR (3–7 WU), the DPG_{NEG} cohort is characterized by lower RAP, and higher tricuspid annular positive systolic excursion (TAPSE), reflecting a state of less pronounced right heart loading and remodelling advocating for milder haemodynamic derangements in the DPG_{NEG} group. This, together with the lower event rate in the DPG_{NEG} as compared with the DPG 0–7 mmHg cohort further supports the concept that DPG_{NEG} in large part results from high V-waves shifting the DPG towards lower values, and suggests limited pre-capillary changes.

In our study, neither the PVR nor the TPG was associated with worse outcome. Furthermore, combining TPG and PVR with DPG failed to demonstrate significant prognostic value ($P = 0.223$ and $P = 0.195$, respectively). This observation stands in contrast to previous results and might be partly related to differences in patient profile. Indeed, as compared with the report by Tampakakis *et al.*, the occurrence of ischaemic heart disease was much higher in our study;[8] additionally, our patient cohort comprised older patients than those studied by Tampakakis *et al.* or Tedford *et al.*[8,9] Finally, the follow-up period was shorter in our study. The constellation of the aforementioned issues as well as the fact that our study comprised fewer patients might account for this discrepancy.

Limitations

Heterogeneity might be considered as comprising a limitation of the current study as catheterizations were performed in two different centres. However, all studies in India were performed in the presence of A.M. who was responsible for the standardization of the studies in the two centres; additionally, the same technical equipment and catheters were used at both sites. Patient characteristics as well as haemodynamics of the two studied cohorts are also rather divergent, as demonstrated in *Table 1* (e.g. patients with AF, hypertension, or ischaemic heart disease were excluded from the MS but not the PH-LHD group); however, as the objective of the present study was not to assess the influence of AF or other co-morbidities on the DPG, but rather to assess the effect of the V-wave amplitude on the DPG measurement, we believe that despite the patients' heterogeneity, the haemodynamic essence of our hypothesis is still addressed. Our cohort comprised patients with PH-LHD (including both preserved and reduced EF) and MS, in which respect it is different from previous comparable studies.

Indeed, pre-capillary involvement as defined by DPG ≥7 mmHg was more frequent in MS patients (20.2%). However, the prevalence of Cpc-PH in the PH-LHD group was 13.6% that is comparable with previous studies (8–16%).[6,8,9] Finally, the current study was performed on haemodynamically stable patients, implying that our findings might not be valid in a state of decompensated acute HF.

Conclusion

The present study verifies the recently observed high frequency of DPG_{NEG}. We propose an applicable physiological explanation for this haemodynamic finding demonstrating a significant inverse association of the V-wave amplitude in the PAWP waveform with the DPG in patients with low PVR. Using direct LAP measurements, we show that the occurrence of DPG_{NEG} is clearly not reflecting methodological inaccuracies; rather it largely represents the augmented disproportionate phasic LAP transmission. Finally, DPG_{NEG} in patients with PH-LHD appears to be associated with milder haemodynamic derangements and better 2-year prognosis compared with patients with DPG within the normal positive range.

Conflict of interest: The authors have no conflict of interest to declare.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Methods and Results.

Figure S1 Flowchart demonstrating the patient enrolment process and haemodynamic classification.

Figure S2 Representative pressure tracings illustrating the influence of V-waves on the DPG value.

Figure S3 Receiver operator characteristics (ROC) analysis of the prognostic ability of the V-wave ($PAWP_V$) for identifying a ΔPG >12 mmHg in patients with pulmonary vascular resistance (PVR) <3 Wood units.

Table S1 Comparison of negative and positive DPG groups in MS and LHD patients with a pre-defined PVR range of 3–7 WU.

Table S2 Alternative PAWP measurements and DPG calculation.

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