Research Article

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Hemodynamics of the diastolic pressure gradients in acute heart failure: implications for the diagnosis of pre-capillary pulmonary hypertension in left heart disease

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Abstract

The diastolic pressure gradient (DPG) has been proposed as the metric of choice for the diagnosis of pulmonary vascular changes in left heart disease. We tested the hypothesis that this metric is less sensitive to changes in left atrial pressure and stroke volume (SV) than the transpulmonary gradient (TPG). We studied the effect of dynamic changes in pulmonary capillary wedge pressure (PCWP), SV, and pulmonary artery capacitance (PAC) on DPG and TPG in 242 patients with acute heart failure undergoing decongestive therapy with continuous hemodynamic monitoring. There was a close impact of PCWP reduction on TPG and DPG, with a 0.13 mmHg (95% confidence interval [CI] 0.07–0.19, $P < 0.0001$) and 0.21 mmHg (95% CI 0.16–0.25, $P < 0.0001$) increase for every 1 mmHg decrease in PCWP, respectively. Changes in SV had a negligible effect on TPG and DPG (0.19 and 0.13 mmHg increase, respectively, for every 10-mL increase in SV). Heart rate was positively associated with DPG (0.41-mmHg increase per 10 BPM [95% CI 0.22–0.60, $P < 0.0001$]). The resistance-compliance product was positively associated with both TPG and DPG (2.65 mmHg [95% CI 2.47–2.83] and 1.94 mmHg [95% CI 1.80–2.08] for each 0.1-s increase, respectively). In conclusion, DPG is not less sensitive to changes in left atrial pressure and SV compared with TPG. Although DPG was not affected by changes in PAC, the concomitant increase in the resistance-compliance product increases DPG.

Keywords

heart failure, diastolic pulmonary vascular pressure gradient, hemodynamics, pulmonary hypertension

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Introduction

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), often related to disease severity and clinical outcomes.[1,2] Passive backward transmission of filling pressures is the initial mechanism leading to PH-LHD. However, a considerable proportion of patients with LHD may develop another superimposed component, combining increased pulmonary vascular resistance (PVR) secondary to complex structural and functional abnormalities in the pulmonary vasculature,[3–5] that is associated with clinical deterioration and poorer outcomes.[3,4,6]

Although accurate differentiation between pre- and post-capillary PH is clinically important, the best hemodynamic definition for pre-capillary PH in the setting of LHD has been elusive. In some studies, PVR was used to identify high-risk patients with PH-LHD,[4,7] while others used elevated trans-pulmonary gradient (TPG).[3,6] The later parameter has been criticized as being sensitive to changes in stroke volume (SV) and filling pressures.[8,9] More recently, the diastolic pressure gradient (DPG) has been proposed as a better marker of changes in the pulmonary circulation in LHD.[8,10]

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In several studies, DPG failed to predict mortality in patients with PH-LHD.[11–13] These results suggest that role of the DPG as metric of choice for assessing pre-capillary PH should be further explored.[14]

We sought to determine whether DPG is less susceptible to changes in filling pressures and SV than the TPG. To this end, we studied the dynamic effects of changes in pulmonary capillary wedge pressure (PCWP) and SV on DPG and TPG during volume unloading and vasodilator therapy in patients with acute heart failure.

Methods

Patients

The study population included patients enrolled in the VMAC study: a randomized, multicenter trial comparing the hemodynamic and clinical effects of nesiritide to nitroglycerin in patients with acute heart failure.[15] The study was approved by all participating centers' institutional review boards for clinical investigation and written informed consent was obtained from each study participant before study entry.

Hemodynamic evaluation

In the VMAC trial, the randomization was stratified based on the use a right heart catheter to manage the patient.[15] In the catheterized group, PCWP and pulmonary artery pressures were measured at baseline, 15 and 30 min, and at 1, 2, 3 6, 9, 12, and 24 h, and in some patients at later timepoints.[15] Cardiac output (CO) was measured at baseline, 1, 3, and 24 h.

The transpulmonary gradient (TPG) was defined as the difference between the mean pulmonary artery pressure (mPAP) and the PCWP. Diastolic pressure gradient (DPG) was defined as diastolic PAP (dPAP) minus mean PCWP (mPAP), with a value $\geq$ 7 mmHg considered elevated.[10] PVR was calculated using standard formulas. Pulmonary artery capacitance (PAC) was estimated as the ratio between SV and the pulmonary pulse pressure (PP). The product of pulmonary resistance and compliance was defined as the RC time.[16]

Hemodynamic definitions of PH

The hemodynamic classification of patients was performed as follows: PH-LHD was defined as PCWP >15 mmHg and mPAP $\geq$25 mmHg. Isolated post-capillary PH (Ipc-PH) was defined as PH-LHD with DPG <7 mmHg and/or PVR $\leq$3 WU. Combined post-capillary PH (Cpc-PH) was defined as DPG $\geq$7 mmHg and/or PVR >3 WU.[10]

Statistical analysis

Continuous variables are presented as mean $\pm$ SD or median with 25th and 75th percentiles; categorical variables are presented as frequencies and percentages. Baseline characteristics of the groups were compared using an unpaired t test for continuous variables and by the χ^2 statistic for noncontinuous variables (or Fisher's exact test, where appropriate).

The relationship between hemodynamic measurements over time was analyzed with the use of repeated-measures, mixed-effects linear regression models with patient-specific random-intercept terms and an unstructured within-patient residual covariance structure. Each model also included the time of the hemodynamic measurement, the interaction between time and the relevant hemodynamic measurement, and baseline value was included as a covariate.

The dependent variables for each mixed model analysis were sPAP, mPAP, dPAP, TPG, DPG, PAC, and RC time. We first examined the longitudinal change in sPAP, mPAP and dPAP associated with PCWP change. We then evaluated the influence of SV on the TPG-PCWP and DPG-PCWP associations. Next, we investigated the effect of heart rate on DPG and the influence of PAC and RC time on TPG and DPG. Missing hemodynamic measurement were <5% of the total observations and were assumed to be missing at random.

A non-linear least-square estimation procedure was used to explore the relationship between PAC and PVR as previously described.[6] Analysis of covariance (ANCOVA) with interaction terms was used to formally compare the slopes of resistance–compliance curves after linearization with log transformations.[6] Finally, we analyzed the relationship between PCWP and the occurrence of negative DPG values.

Differences were considered statistically significant at the two-sided $P < 0.05$ level. All statistical analyses were performed using Stata version 15.1 (College Station, TX, USA).

Results

Of the total 489 randomized and treated patients, 246 were in the catheterized stratum. Four patients were excluded due to missing hemodynamic data. Demographic, clinical, and hemodynamic characteristics of the remaining 242 patients according to DPG are shown in Table 1.

Patients with elevated DPG were younger, had lower left ventricular ejection fraction, and a trend toward higher estimated GFR. They presented with higher heart rate and were less likely to receive β-blockers. Patients with elevated DPG had higher sPAP, dPAP, PVR, and TPG.

Changes in dPAP and sPAP during decongestive therapy

We first studied the relationship between dPAP, mPAP, and sPAP and changes in PCWP during diuretic and vasodilator therapy. Of the possible 2420 observations for each parameter at the 10 timepoints, missing dPAP, sPAP, and PCWP data occurred in 2%, 2%, and 4%, respectively.

Figure 1a shows the changes in dPAP, mPAP, and sPAP over time and demonstrates a proportional reduction of

Table 1. Baseline characteristics according to post-treatment DPG.*

Characteristics	DPG < 7 mmHg (n = 205)	DPG ≥ 7 mmHg (n = 37)	*P* value
Age (years)	61 ± 14	55 ± 11	0.007
Female gender	51 (25)	7 (19)	0.43
Body mass index (kg/m^2)	29 ± 6	29 ± 6	0.76
Ischemic etiology of heart failure	115 (56)	16 (43)	0.15
Left ventricular ejection fraction (%)	26 ± 13	20 ± 10	0.02
Diabetes mellitus	101 (49)	13 (35)	0.11
Atrial fibrillation	74 (36)	9 (24)	0.17
Baseline heart rate (beats/min)	82 ± 16	90 ± 13	0.006
Systolic blood pressure (mmHg)	118 ± 20	119 ± 21	0.90
Baseline creatinine (mg/dL)	1.5 [1.1–1.9]	1.3 [0.9–1.8]	0.21
Estimated GFR (mL/min per 1.73 m^2)	51 [33–71]	61 [41–86]	0.07
Randomized to nesiritide	162 (79)	22 (59)	0.01
Cardiac medications			
Digoxin	93 (45)	23 (62)	0.06
ACE inhibitors / ARB	150 (73)	29 (78)	0.51
β-blockers Spironolactone	56 (22)	3 (8)	0.05
Hemodynamic variables	59 (29)	9 (24)	0.58
Right atrial pressure (mmHg)	15 ± 7	16 ± 7	0.51
Pulmonary capillary wedge pressure (mmHg)	28 ± 6	27 ± 6	0.19
Cardiac output (L/min)	4.3 ± 1.6	4.2 ± 1.7	0.72
Cardiac index (L/min/m^2)	2.2 ± 0.7	2.1 ± 0.7	0.26
Stroke volume index (mL/m^2)	54 ± 20	49 ± 22	0.15
Systolic pulmonary artery pressure (mmHg)	58 ± 12	67 ± 13	0.0001
Diastolic pulmonary artery pressure (mmHg)	27 ± 6	36 ± 7	<0.0001
Pulmonary vascular resistance (WU)	2.5 ± 1.7	5.5 ± 2.7	<0.0001
Transpulmonary gradient (mmHg)	9.5 ± 5.2	19.7 ± 4.0	<0.0001

*Values are presented as n (%), mean ± SD, or median [interquartile range].

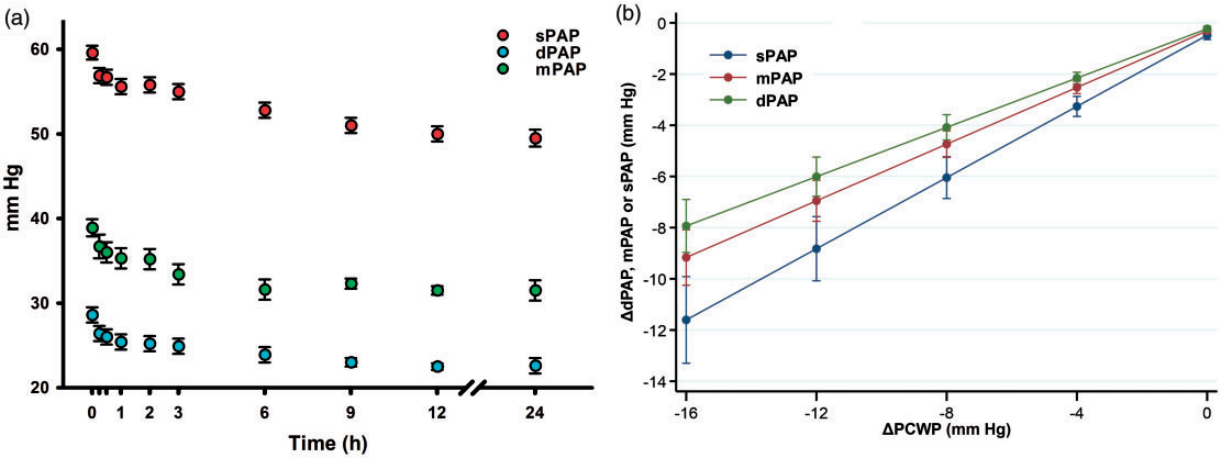

Fig. 1. (a) Changes in systolic and diastolic pulmonary arterial pressures during diuretic and vasoactive therapy. (b) Relationship between the change in PCWP and the change in pulmonary pressures (sPAP, mPAP, and dPAP). Error bars represent the mean with 95% confidence intervals.

dPAP and sPAP. During the first 24 h, dPAP, mPAP, and sPAP decreased by 6.1 ± 6.9 mmHg, 7.4 ± 7.9 mmHg, and 10.2 ± 12.2 mmHg, respectively. Linear mixed modeling demonstrated that the curves describing the changes in sPAP, mPAP, and dPAP in response to the reduction in PCWP were nearly parallel (Fig. 1b). For every 1 mmHg change in PCWP, sPAP, mPAP, and dPAP changed by 0.70 mmHg (95% confidence interval [CI] 0.58–0.81, $P < 0.0001$), 0.55 (95% CI 0.48–0.62, $P < 0.0001$), and 0.48 mmHg (95% CI 0.41–0.55, $P < 0.0001$), indicating a close impact of PCWP reduction on mPAP and dPAP.

Relation of TPG/DPG with PCWP and SV

Because the TPG has been considered to be sensitive to changes in SV,[8] we estimated the impact of SV on TPG and DPG responses to the change in PCWP using hemodynamic measurement at baseline, 1, 3, and 24 h. Of the possible 968 observations for each parameter at the four timepoints, missing DPG, TPG, SV, and PCWP data occurred in 4%, 4%, 2%, and 4% of cases, respectively.

The mean SV over all measurements was 56 ± 19 mL (range 22–107 mL). During the first 24 h, there was a small but significant increase in SV (53 ± 20 to 58 ± 20 mL, $P < 0.0001$). Results of the linear mixed model used to study the changes in TPG and DPG in response to the reduction in PCWP and SV changes are shown in Fig. 2, with fitted lines for the median SV value and the 10th and 90th percentiles.

There was an inverse association between TPG and PCWP such that TPG increased by 0.13 mmHg for every 1 mmHg decrease in PCWP (95% CI 0.07–0.19, $P < 0.0001$). In the unadjusted model, SV had a small effect on TPG, with a 0.19 mmHg increase for every 10 mL increase in SV (95% CI 0.01–0.38, P 0.036). However, SV was not significantly associated with TPG when PCWP was added to the model (P 0.37).

The effect of PCWP reduction on DPG was also significant (0.21 mmHg increase for every 1 mmHg decrease in PCWP, 95% CI 0.16–0.25, $P < 0.0001$) with a minor effect of SV in the unadjusted model (0.13 mmHg increase for every 10 mL increase in SV) and a non-significant effect (P 0.32) when PCWP was included in the model (Fig. 2a). Similar results were obtained when TPG and DPG changes were modeled versus PCWP and SV changes (Fig. 2b). The impact of SV changes was negligible.

There was no interaction between the effect of nitroglycerine or nesiritide on PCWP with regard to their effects on TPG (P 0.15) and DPG (P 0.81). For example, for every 1 mmHg decrease in PCWP, TPG increased by 0.23 mmHg (95% CI 0.07–0.40, P 0.006) in the nitroglycerine group and by 0.1 mmHg (95% CI 0.04–0.13, P 0.006) in the nesiritide group.

Effect of heart rate and PVR on DPG

Heart rate (included in the model as a time-dependent variable) was positively associated with DPG, with a 0.41 mmHg increase for a 10 BPM increase (95% CI 0.22–0.60, $P < 0.0001$). There was no interaction between the effect of PCWP and heart rate (P 0.88), indicating that the effect of heart rate on DPG was similar at all levels of PCWP.

PVR was also positively associated with DPG (1.93 mmHg increase in DPG for 1 WU increase PVR, 95% CI 1.40–2.45, $P < 0.0001$). Figure 3 depicts the change in DPG as a function of PCWP and PVR. With low PVR (≤3 WU), DPG is consistently <7 mmHg at all PCWP values. However, with elevated PVR (>3 WU), DPG can be <7 mmHg or even negative when PCWP is elevated. As a result, with the reduction of PCWP from baseline to the 24-h timepoint, the number of patients

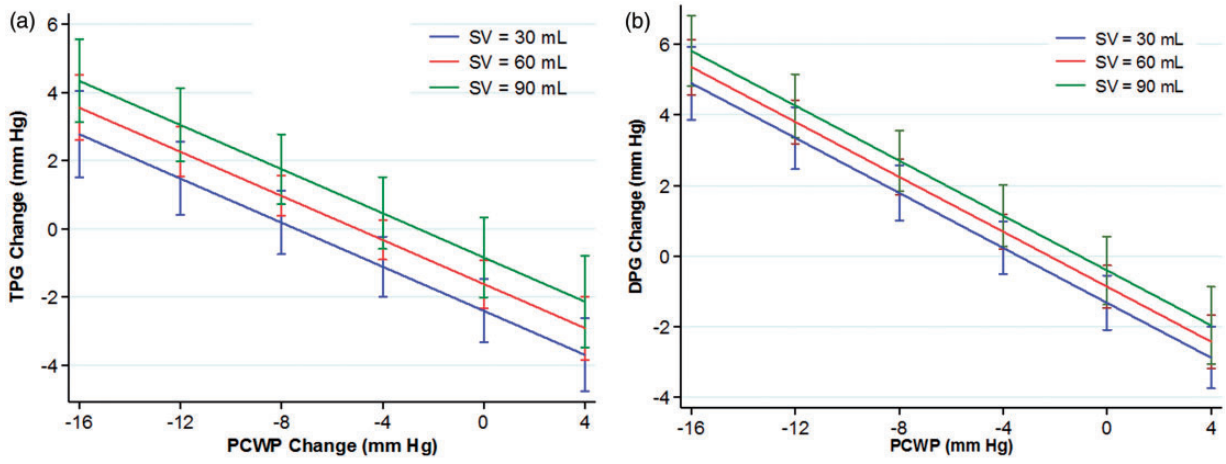

Fig. 2. Relationship of stroke volume (SV) and pulmonary capillary wedge pressure (PCWP) with the transpulmonary pressure gradient (TPG) and the diastolic pressure gradient (DPG). (a) Graph showing absolute TPG, DPG, PCWP, and SV values. (b) Graph showing changes in TPG, DPG, PCWP, and SV values. Separate lines were fitted for TPG and DPG at the median SV and two extremes (10th and 90th percentile) of SV.

with elevated DPG increased from 37 (15.3%) to 67 (27.7%), despite an overall reduction in PVR.

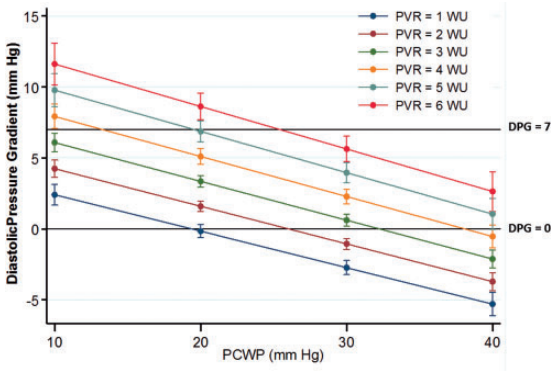

Fig. 3. Relationship between DPG and PCWP at different levels of PVR. At high PCWP, DPG may be low (<7 mmHg) even when PVR is high.

Relationship between TPG, DPG, and RC time

During treatment and reduction of PCWP, PVR decreased (0.18 ± 0.13 to 0.16 ± 0.11 mmHg·s^{-1}·mL^{-1}, P 0.01; 3.06 ± 2.25 to 2.77 ± 1.71 WU) while PAC increased (1.84 ± 1.02 to 2.50 ± 1.64 mL/mmHg, $P < 0.0001$). There was a shift of the hyperbolic curve upward and to the right (Fig. 4a, $P < 0.001$ for the difference of the log-transformed curves by ANCOVA).

Linear mixed models were fitted to determine the relationship between PAC, RC time, and both TPG and DPG. Figure 4b shows that an increase in PAC was associated with a reduction of TPG (1.46 mL/mmHg reduction in TPG [95% CI 0.98–1.93, $P < 0.0001$] for a 1 mL/mmHg increment in PAC). The association of PAC with DPG was weaker and of borderline significance (0.39 mL/mmHg increase in DPG for 1 mmHg increase in PAC, 95% CI −0.01–0.79, P 0.052).

The changes in PAC and PVR resulted in a significant increase in RC time from baseline to the 24-h timepoint (0.28 ± 0.14 s to 0.35 ± 0.20, P 0.0016). The increase in the RC time that occurred with the reduction of PCWP was associated with an increase of both TPG and

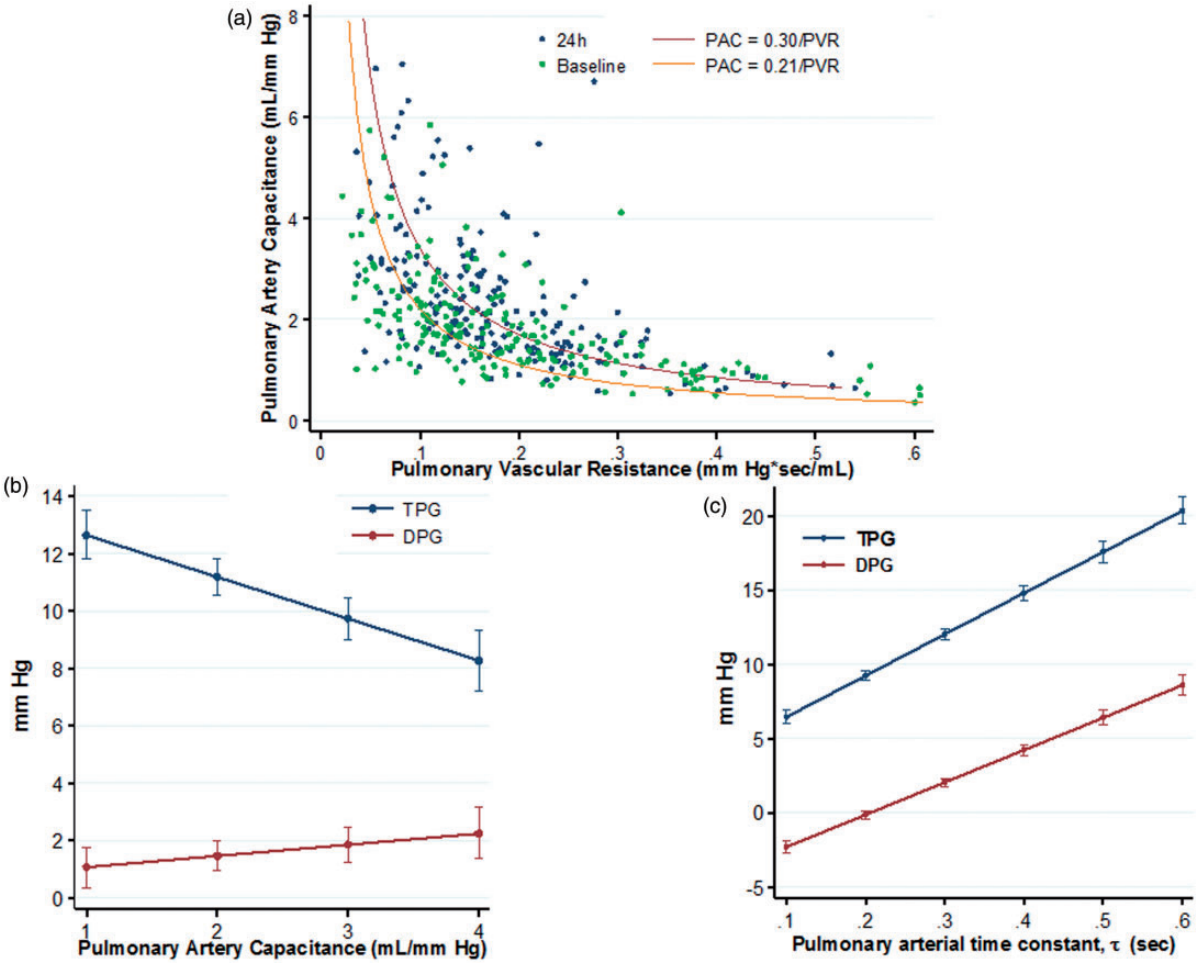

Fig. 4. (a) Scatterplots and curve fits of PVR vs. pulmonary arterial compliance demonstrate that an upward/rightward shift of the inverse hyperbolic relationship from baseline to 24 h. (b) PCWP is inversely related to TPG but has no significant effect on DPG. (c) The RC time (resistance-compliance product) is positively related to TPG and DPG. Therefore, both TPG and DPG increase during decongestive therapy.

DPG (2.65 mmHg [95% CI 2.47–2.83] and 1.94 mmHg [95% CI 1.80–2.08] for each 0.1-s increase in RC time, respectively (Fig. 4c).

Negative DPG and the relationship between PCWP and dPAP

Negative DPG values were recorded in 28.8% of all DPG measurements. However, there was a progressive decline in negative DPG values over time with the reduction in PCWP (Fig. 5), with 38.4% and 18.4% of the patients demonstrating negative DPG at baseline and 24 h, respectively.

Discussion

The clinical differentiation between Ipc-PH and Cpc-PH is patients with PH-LHD is challenging. Recently, it has been suggested that the pressure gradient between the dPAP and PCWP (DPG) is less dependent on left atrial pressure, SV, and pulmonary arterial compliance than the TPG; therefore, an elevated DPG may be a better indicator of a pre-capillary component in PH-LHD.[8] However, these assumptions were largely based on theoretical considerations[8] and data extrapolated from studies in healthy individuals,[17] and were not adequately tested in patients with PH-LHD.

In the present study, we used a cohort of acute LHD patients undergoing diuretic and vasoactive therapy to assess dynamic changes in DPG that occurred in response to changes in PCWP, SV, and RC time of the pulmonary circulation. Our results demonstrate a similar response of DPG and TPG to changes in filing pressures, CO, and RC time.

Effect of PCWP reduction on sPAP and dPAP

It has been proposed that during volume unloading sPAP and mPAP may decrease in parallel to PCWP, whereas dPAP remains relatively unaffected.[9] In the present study, crude data showed that sPAP and dPAP declined in parallel, and a mixed model demonstrated a remarkable similarity in the slope relating mPAP and dPAP change with that of PCWP.

Transmission of PCWP upstream to the pulmonary vasculature can be influenced by several factors including pulmonary closing pressure, distention and recruitment of additional vascular channels, and presence of pulmonary vasoconstriction or remodeling. During diastole, the pulmonary blood flow may drop to zero, making the dPAP insensitive to changes in left atrial pressures. This is less likely to occur in LHD because PCWP is elevated well above the normal range. As left atrial pressure increases, it exceeds the vascular closing pressure of a progressively larger fraction of the pulmonary circulation, and a larger proportion of left atrial pressure is transmitted upstream. This may explain the similarity in the slopes relating mPAP and dPAP to PCWP. Importantly, the similarity in the response of mPAP and dPAP to the changes in PCWP dictates that the corresponding changes in TPG and DPG will also be similar.

Effect of SV on TPG and DPG

In a classic paper, Harvey et al. concluded that SV has no discernible effect on the dPAP, and that its contribution to sPAP is small; they predicted that an increase in SV of 50 mL will increase sPAP by 4 mmHg.[17] These estimates were based on studies in healthy volunteers, at rest and at various levels of exercise where CO increased up to 25–30 L/min.[17] However, in a subsequent study from Harvey's group, a significant positive correlation was found between DPG and CO in a dog model.[18] More recently, Naeije et al. also proposed that changes in SV might affect the TPG whereas DPG is expected to remain unchanged.[8]

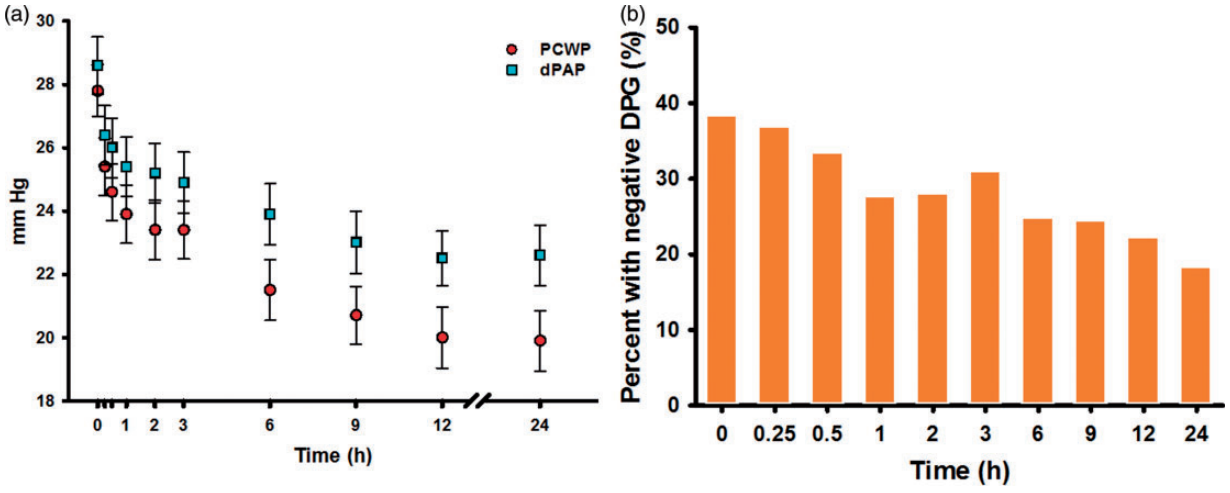

Fig. 5. (a) Changes in dPAP and PCWP over time. (b) Bar graph showing the proportion of negative DPG measurements with the reduction of PCWP over time.

In patients with acute heart failure receiving vasodilator therapy, the increases in SV that occurs due to the reduction in filling pressures are relatively small and are secondary to reduced afterload on the ventricles and a reduction in effective mitral regurgitant fraction.[19–21] In this scenario, the increase in SV is associated with a reduction in PCWP and mPAP. This is different from normal exercising individuals, where a large increase in SV and pulmonary flow and a large reduction in PVR are the major hemodynamic change, while PCWP and mPAP increase.[22]

In the current study of patients with HFrEF, changes in TPG and DPG were predominantly determined by changes in PCWP. Even relatively large changes in SV that may occur in a minority of patients were not associated with any clinically significant change in TPG or DPG, indicating that these parameters are insensitive to changes in SV. Thus, in hemodynamic studies attempting to differentiate between isolated Icp-PH and Cpc-PH (which are typically performed at rest), clinically pertinent SV changes are unlikely to lead to erroneous conclusions.

As in previous studies,[18,23] we found a positive association between heart rate and DPG. Although the magnitude of the heart rate effect was not large, changes in rate may need to be considered when interpreting DPG, as small changes may reclassify patients into Ipc-PH or Cpc-PH.

PAC, RC time, and DPG

Elevation of PCWP shifts the PAC-PVR curve downward and to the left and reduces the RC time.[6,24] During decongestive therapy, we observed an increase in PAC, which may be secondary to PCWP reduction[25] but also due to volume correction.[26]

Naeije et al. argued that the disproportionate decrease in PAC (relative to PVR) and the shorter RC time in the presence of increased PCWP may be a cause of increased TPG without coexistent pulmonary vasoconstriction or remodeling.[8] Indeed, our results demonstrate that a decrease in PAC is associated with increasing TPG, while DPG remains almost unaffected (Fig. 5b). Because a decrease in arterial compliance can result from an increase in mPAP without a true change in the elastic properties of the pulmonary arterial wall,[16] TPG increases with a reduction in PAC. This is not necessarily a spurious elevation in TPG as a decrease in PAC is associated with increased mortality in PH-LHD.[6,25]

Based on the present data, an increase of ~1.5 mm Hg in TPG requires a 1 mL/mmHg decrease in PAC, which represents a relatively large reduction. Consequent to the hyperbolic shape of the PAC-PVR curve, such changes in PAC can occur mainly in patients with low baseline PVR (i.e. those who would not be suspected as having Cpc-PH).

Because the RC time represents the exponential pressure decay in the pulmonary artery during diastole, it is mathematically coupled with dPAP and PCWP and hence with DPG.[16,27] In PH-LHD, any change in PAC is not limited to TPG because of the obligatory corresponding change in RC time. For example, during decongestion, PAC increases more than PVR decreases. The overall effect is the prolongation of the RC time, which equates to slower pressure decay in diastole and an increase in DPG (Fig. 5c).

Negative DPG values

Tampakakis et al. reported that 36% of the patients with PH-LHD had negative DPG values. Low DPG was associated with higher PCWP and with poor outcome.[11] We observed a similar proportion of negative DPG values in the acute heart failure setting. Our results also demonstrate that as PCWP falls, the proportion of patients with negative DPG also declines.

The high percentage of patients with negative DPG observed in acute and chronic HF patients raises a concern regarding potential misclassification of PH subgroup when using this parameter. Our results indicate that patients with high PCWP, and to a lesser extent with tachycardia, are expected to have low or negative DPG values even when PVR is elevated. This finding emphasizes the limitations of using DPG as an indicator for Cpc-PH.

Negative DPG values have been attributed to motion artefacts and inadequate dynamic responses due to over damping or under damping.[8] If this hypotheses were true, we would not necessarily expect a systematic relationship between negative DPG values and the severity of PCWP elevation. Furthermore, negative DPG values are also common when based on left ventricular end diastolic pressure measurements,[28] where overestimation of PCWP is not a concern.

DPG and prognosis

Although recommended by recent guidelines for the differentiation of Ipc-PH and Cpc-PH,[10] the diagnostic and prognostic value of DPG remains controversial. Tampakakis et al. showed in a large sample of patients with PH-LHD that the DPG did not discriminate survivors from non-survivors.[11] Tedford et al. demonstrated that an elevated DPG had no effect on post-transplant survival in patients with PH and an elevated TPG and PVR.[12] Recently, Gerges et al. reported that patients with DPG $\geq$ 7 mmHg and either HFpEF or HFrEF had an increased mortality.[29] By contrast, Assad et al. reported similar mortality in Cpc-PH and Ipc-PH when defined by using DPG but increased mortality in Cpc-PH defined according to PVR alone.[13] These inconsistencies in the prognostic significance of DPG-based definitions of Cpc-PH may stem from the aforementioned limitations of DPG.

Study limitations

Our study has some limitations that merit emphasis. First, the present analysis is retrospective and thus the results must be regarded as hypothesis generating and exploratory and

require validation in other studies. Our cohort consisted only of patients with reduced ejection fraction.

Hemodynamic measurements in the present study were performed in expert centers according to individual institutional practice. Therefore, although PAWP measurements during a brief breath-hold at end-expiration variation is standard, differences in zero levelling between centers, manual measurements, or differences due to attempts to correct for waveform artifacts versus automated digital pressure measurements and other parameters can occur.[30] Therefore, the results should be considered as representing real-world practice in the setting of acute heart failure and may lack precision. No data were available with regard to specific conditions that might have contributed to negative DPG values (e.g. severe mitral regurgitation).[31]

Conclusion

In the present study, we were unable to demonstrate that DPG is less sensitive to changes in PCWP and SV than TPG. CO had a negligible effect on both DPG and TPG. Although DPG was not affected by changes in pulmonary arterial compliance, the concomitant increase in RC time was associated with increased DPG. The validity of DPG must be more clearly demonstrated before it can be employed as a diagnostic and prognostic metric for Cpc-PH in patients with PH-LHD.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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