Characteristics of cardiopulmonary exercise testing in patients with combined post- and pre-capillary pulmonary hypertension due to left heart disease

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Article

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Abstract

Pulmonary hypertension (PH) is a common and morbid complication of left heart disease (LHD), comprising two subtypes: (1) isolated post-capillary PH (Ipc-PH) and (2) combined post-capillary and pre-capillary PH (Cpc-PH). Knowledge of physiological characteristics distinguishing Cpc-PH from Ipc-PH remains limited. Therefore, this study aimed to assess the utility of cardiopulmonary exercise test (CPX) variables in detecting Cpc-PH. Among 105 consecutive patients with LHD (age: 55 ± 13 years; male/female = 79/26) who underwent right heart catheterization and CPX, 37 (35%) were classified as PH-LHD. Ipc-PH (n = 23) was defined as diastolic pulmonary pressure gradient (DPG) < 7 mmHg and/or pulmonary vascular resistance (PVR) ≤ 3 Wood units (WU), whereas Cpc-PH (n = 14) was defined as DPG ≥ 7 mmHg and/or PVR > 3 WU. Patients with Cpc-PH had a significantly lower peak $PETCO_2$ (Non-PH/Ipc-PH/Cpc-PH = 38.3 ± 6.7 vs. 35.6 ± 5.9 vs. 32.7 ± 4.0 mmHg, p = 0.006), higher VE vs. VCO_2 slope, and lower $\Delta VO_2/\Delta WR$ than those with Ipc-PH and non-PH. Logistic regression analysis revealed that peak $PETCO_2$ was an independent predictor of Cpc-PH (odds ratio: 0.854, 95% confidence interval [CI]: 0.757–0.962, p = 0.009). Peak $PETCO_2$ was the optimal predictor of Cpc-PH in the ROC analysis (AUC: 0.747, 95% CI: 0.640–0.854, p = 0.003). In conclusion, peak $PETCO_2$ was associated with Cpc-PH in patients with LHD.

Introduction

Pulmonary hypertension (PH) is a common and morbid complication of left heart disease (LHD), comprising two subtypes: (1) isolated post-capillary PH (Ipc-PH) and (2) combined post-capillary and pre-capillary PH (Cpc-PH)[1, 2]. Pathologically and genetically, Cpc-PH is considered to possess characteristics intermediate between pulmonary arterial hypertension (PAH) and LHD[3–5] and have a worse prognosis than that of Ipc-PH. However, knowledge regarding the clinical or physiological characteristics that distinguish these two subphenotypes remains limited[6]. The efficacy of pulmonary vasodilators in Cpc-PH has recently been explored[7, 8]. Despite the increased importance in the detection and differentiation of Cpc-PH to enable a tailored approach to PH treatment, the invasive evaluation of pulmonary hemodynamics remains mandatory.

The cardiopulmonary exercise test (CPX) is a well-established noninvasive test for assessing functional capacity and exercise limitation. Based on pathophysiology, it provides mechanistic insights, important information on gas exchange, ventilatory efficacy, and cardiac function during exercise[9, 10]. Peak oxygen consumption (peak VO_2), which reflects the cardiac output (CO) during exercise, and other ventilatory variables, such as the ventilation/carbon dioxide production relationship slope (VE vs. VCO_2 slope), remain the most frequently applied variables in CPX and have been used as markers of disease severity and prognosis in patients with heart failure (HF) and PAH[11–14]. In terms of CPX, PAH is characterized by a lower peak VO_2, marked hyperventilation, low end-tidal partial pressure of carbon dioxide ($PETCO_2$), and elevated VE vs. VCO_2 slope[14, 15]. The combination of a low $PETCO_2$ and high ventilatory equivalents for carbon dioxide (VE/VCO_2) at the anaerobic threshold (AT) has been considered suggestive of PH[16].

According to previous reports on the differentiation of Cpc-PH, the usefulness of various ventilatory parameters, such as the VE/VCO_2 at the AT, $PETCO_2$, dead-space ventilation to tidal ventilation (VD/VT), and lowest VE/VCO_2%pred, has been proposed; however, no consensus has been reached[17, 18].

The examination of CPX variables in patients with Cpc-PH potentially provides mechanistic insights that will enhance our understanding of its pathophysiology and facilitate the detection of early abnormal adaptations leading to Cpc-PH. Therefore, this study aimed to assess the utility of CPX variables in the non-invasive detection of Cpc-PH, which is considered to possess characteristics of both PAH and LHD.

Results

General characteristics

The 105 enrolled patients with LHD who underwent right heart catheterization (RHC) and CPX were predominantly male (75%), with a mean age of 55 ± 13 years and mean left ventricular ejection fraction (LVEF) of 39 ± 14%. Overall, 37 patients (35%) were classified as PH-LHD. Among them, 23 patients (22%) had Ipc-PH, and 14 (13%) had Cpc-PH (Fig. 1). The general characteristics of the Non-PH, Ipc-PH, and Cpc-PH groups are shown in Table 1. There were no significant differences in age, LHD etiology, hemoglobin level, or LVEF among the three groups. Patients in the Cpc-PH group were predominantly male, and they exhibited higher brain natriuretic peptide levels than those in the Non-PH and Ipc-PH groups.

Table 1
Baseline characteristics of the study patients.

	Non-PH (n = 68)	Ipc-PH (n = 23)	Cpc-PH (n = 14)	p-value	Non-PH vs. Ipc-PH	Non-PH vs. Cpc-PH	Ipc-PH vs. Cpc-PH
Age, years	55 ± 13	56 ± 13	56 ± 13	0.859	0.868	0.946	0.996
Sex (male/female)	46/22	22/1	11/3	0.015			
BMI, kg/m^2	22.5 [20.3, 25.5]	22.2 [20.7, 27.0]	26.0 [22.4, 26.6]	0.301			
Etiology							
Cardiomyopathy, n (%)	43 (63%)	15 (65%)	7 (50%)	0.531			
Ischemia, n (%)	7 (10%)	3 (13%)	3 (21%)	0.454			
Valvular, n (%)	9 (13%)	3 (13%)	1 (7%)	0.990			
Others, n (%)	9 (13%)	2 (9%)	3 (21%)	0.531			
BNP, ng/mL	164 [71, 288]	336 [195, 768]	339 [225, 653]	0.010	0.007	0.012	1.000
Hemoglobin, g/dL	14.3 ± 2.0	13.8 ± 2.5	14.9 ± 2.2	0.351	0.632	0.630	0.322
LVEF, %	37 [30, 51]	36 [29, 47]	29 [23, 43]	0.152			
Hemodynamic data							
PAWP, mmHg	10 [7, 13]	21 [18, 23]	21 [17, 26]	< 0.001	< 0.001	< 0.001	1.000
Systolic PAP, mmHg	29 [22, 32]	43 [40, 47]	51 [45, 59]	< 0.001	< 0.001	< 0.001	0.958
Diastolic PAP, mmHg	11 [8, 13]	21 [18, 22]	22 [18, 29]	< 0.001	< 0.001	< 0.001	1.000

Values are reported as mean ± SD or median (25th, 75th interquartile range), where appropriate.

BMI: body mass index, BNP: brain natriuretic peptide, CO: cardiac output, Cpc: combined post-capillary and pre-capillary, DPG: diastolic pressure gradient, Ipc: isolated post-capillary, LVEF: left ventricular ejection fraction, PAP: pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, PH: pulmonary hypertension, PVR: pulmonary vascular resistance, RAP: right atrial pressure, RVEDP: right ventricular end-diastolic pressure, SaO_2: arterial oxygen saturation, SvO_2: mixed venous oxygen saturati

	Non-PH (n = 68)	Ipc-PH (n = 23)	Cpc-PH (n = 14)	p-value	Non-PH vs. Ipc-PH	Non-PH vs. Cpc-PH	Ipc-PH vs. Cpc-PH
Mean PAP, mmHg	17 [14, 21]	29 [26, 31]	33 [29, 43]	< 0.001	< 0.001	< 0.001	1.000
RVEDP, mmHg	5 [4, 7]	8 [7, 11]	12 [10, 13]	< 0.001	0.001	< 0.001	0.390
Mean RAP, mmHg	4 [3, 6]	7 [5, 9]	9 [6, 11]	< 0.001	0.002	< 0.001	0.654
DPG, mmHg	1 [-1, 3]	-1 [-2, 2]	1 [-1, 4]	0.102			
SaO_2, %	97 [95, 98]	97 [95, 98]	96 [94, 98]	0.495			
SvO_2, %	72 [69, 74]	67 [61, 72]	61 [57, 68]	< 0.001	0.027	0.001	0.503
CO, L/min	3.8 [3.3, 4.4]	3.8 [2.8, 4.8]	2.8 [2.6, 3.2]	0.015	1.000	0.014	0.047
PVR, Wood units	1.7 [1.2, 2.6]	2.2 [1.8, 2.9]	4.5 [3.3, 6.6]	< 0.001	0.266	< 0.001	0.001
Values are reported as mean ± SD or median (25th, 75th interquartile range), where appropriate.							
BMI: body mass index, BNP: brain natriuretic peptide, CO: cardiac output, Cpc: combined post-capillary and pre-capillary, DPG: diastolic pressure gradient, Ipc: isolated post-capillary, LVEF: left ventricular ejection fraction, PAP: pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, PH: pulmonary hypertension, PVR: pulmonary vascular resistance, RAP: right atrial pressure, RVEDP: right ventricular end-diastolic pressure, SaO_2: arterial oxygen saturation, SvO_2: mixed venous oxygen saturati							

Hemodynamic Parameters

The hemodynamic parameters of the study groups are shown in Table 1. Pulmonary artery wedge pressure (PAWP), pulmonary artery pressure (PAP), and mean right atrial pressure (RAP) in the Ipc-PH and Cpc-PH groups were significantly higher than those in the non-PH group. However, these variables did not differ between the Ipc-PH and Cpc-PH groups. The CO in the Cpc-PH group was significantly lower than that in the non-PH and Ipc-PH groups (Non-PH/Ipc-PH/Cpc-PH = 3.8 [3.3, 4.4] vs. 3.8 [2.8, 4.8] vs. 2.8 [2.6, 3.2] L/min, p = 0.015). Pulmonary vascular resistance (PVR) in the Cpc-PH group was significantly higher than that in the non-PH and Ipc-PH groups (Non-PH/Ipc-PH/Cpc-PH = 1.7 [1.2, 2.6] vs. 2.2 [1.8, 2.9] vs. 4.5 [3.3, 6.6] Wood units (WU), p < 0.001).

Cpx Parameters

The characteristics of the CPX variables according to hemodynamics are listed in Table 2.

Table 2
Exercise parameters.

	Non-PH N = 68	Ipc-PH N = 23	Cpc-PH N = 14	p-value	Non-PH vs. Ipc-PH	Non-PH vs. Cpc-PH	Ipc-PH vs. Cpc-PH
Rest							
HR, bpm	79 [67, 87]	82 [70, 93]	69 [61, 77]	0.031	0.449	0.189	0.025
VO_2, mL/min	223 ± 43	235 ± 48	252 ± 44	0.074	0.510	0.074	0.500
VCO_2, mL/min	197 [169, 219]	213 [180, 254]	200 [177, 252]	0.328			
R	0.90 [0.84, 0.94]	0.89 [0.87, 0.93]	0.85 [0.80, 0.88]	0.025	1.000	0.039	0.031
VE, L/min	9.4 [8.0, 10.6]	10.6 [9.4, 12.0]	10.8 [8.5, 11.3]	0.036	0.063	0.327	1.000
VE/VO_2	43.4 ± 7.7	47.8 ± 11.1	41.5 ± 6.0	0.048	0.081	0.728	0.075
VE/VCO_2	48.3 ± 8.3	52.2 ± 11.1	49.3 ± 6.2	0.193	0.165	0.930	0.585
$PETCO_2$, mmHg	36.7 ± 4.5	35.3 ± 4.6	35.1 ± 3.2	0.264	0.384	0.440	0.992
Anaerobic threshold							
Work rate, watts	50 ± 17	44 ± 14	52 ± 22	0.263	0.297	0.935	0.348
HR, bpm	99 [86, 112]	102 [91, 110]	97 [87, 107]	0.611			
VO_2, mL/min	704 ± 211	641 ± 185	704 ± 187	0.440	0.422	1.000	0.638
VCO_2, mL/min	638 ± 193	584 ± 154	639 ± 190	0.483	0.467	1.000	0.664

Values are reported as mean ± SD or median (25th, 75th interquartile range), where appropriate.

AT: anaerobic threshold, Cpc: combined post-capillary and pre-capillary, HR: heat rate, Ipc: isolated post-capillary, $ETCO_2$: end-tidal partial pressure of carbon dioxide, PH: pulmonary hypertension, R: respiratory exchange ratio, VCO_2: carbon dioxide output, VE: minute ventilation, VO_2: oxygen consumption, $\Delta VO_2/\Delta WR$: the slope of the increase in VO_2 to the increase in the work rate

	Non-PH N = 68	Ipc-PH N = 23	Cpc-PH N = 14	p-value	Non-PH vs. Ipc-PH	Non-PH vs. Cpc-PH	Ipc-PH vs. Cpc-PH
R	0.91 [0.86, 0.94]	0.92 [0.87, 0.97]	0.91 [0.87, 0.95]	0.870			
VE, L/min	22.7 ± 5.0	22.8 ± 5.6	25.4 ± 6.1	0.204	0.998	0.186	0.303
VE/VO_2	33.4 ± 6.4	37.2 ± 10.0	36.9 ± 5.8	0.060	0.099	0.243	0.994
VE/VCO_2	36.8 ± 6.8	40.1 ± 8.5	41.0 ± 7.2	0.059	0.166	0.135	0.936
$PETCO_2$, mmHg	41.6 ± 5.4	39.3 ± 5.5	37.3 ± 4.8	0.012	0.177	0.017	0.510
VO_2 at the AT, mL/min/kg	10.7 [9.0, 12.8]	9.1 [7.6, 10.3]	10.7 [9.1, 11.5]	0.021	0.016	1.000	0.345
Peak							
Work rate, watts	90 ± 32	85 ± 22	92 ± 40	0.718	0.763	0.964	0.745
HR, bpm	124 ± 27	126 ± 25	109 ± 33	0.156	0.982	0.158	0.195
VO_2, mL/min	1074 [867, 1361]	974 [787, 1209]	997 [785, 1255]	0.434			
VCO_2, mL/min	1242 ± 461	1153 ± 403	1206 ± 530	0.721	0.702	0.961	0.938
R	1.11 ± 0.11	1.16 ± 0.11	1.14 ± 0.12	0.245	0.234	0.737	0.861
VE, L/min	45.8 ± 15.5	45.6 ± 13.2	51.0 ± 17.9	0.488	0.999	0.476	0.555
VE/VO_2	42.3 ± 9.0	47.8 ± 11.6	49.5 ± 6.5	0.006	0.041	0.028	0.863
VE/VCO_2	36.9 [32.6, 42.0]	37.4 [34.2, 47.3]	41.8 [39.3, 50.6]	0.017	0.572	0.018	0.442

Values are reported as mean ± SD or median (25th, 75th interquartile range), where appropriate.

AT: anaerobic threshold, Cpc: combined post-capillary and pre-capillary, HR: heat rate, Ipc: isolated post-capillary, $ETCO_2$: end-tidal partial pressure of carbon dioxide, PH: pulmonary hypertension, R: respiratory exchange ratio, VCO_2: carbon dioxide output, VE: minute ventilation, VO_2: oxygen consumption, $\Delta VO_2/\Delta WR$: the slope of the increase in VO_2 to the increase in the work rate

	Non-PH N = 68	Ipc-PH N = 23	Cpc-PH N = 14	p-value	Non-PH vs. Ipc-PH	Non-PH vs. Cpc-PH	Ipc-PH vs. Cpc-PH
$PETCO_2$, mmHg	38.3 ± 6.7	35.6 ± 5.9	32.7 ± 4.0	0.006	0.175	0.008	0.358
Peak VO_2, mL/min/kg	17.7 ± 5.4	14.6 ± 3.8	15.1 ± 4.1	0.018	0.030	0.182	0.951
VE vs. VCO_2 slope	32.5 [28.2, 36.9]	33.9 [29.4, 42.5]	38.2 [34.1, 43.3]	0.043	0.872	0.044	0.519
$\Delta VO_2/\Delta WR$, mL/min/watt	8.4 ± 1.5	7.7 ± 2.1	7.2 ± 1.8	0.029	0.209	0.047	0.731
Values are reported as mean ± SD or median (25th, 75th interquartile range), where appropriate.							
AT: anaerobic threshold, Cpc: combined post-capillary and pre-capillary, HR: heat rate, Ipc: isolated post-capillary, $ETCO_2$: end-tidal partial pressure of carbon dioxide, PH: pulmonary hypertension, R: respiratory exchange ratio, VCO_2: carbon dioxide output, VE: minute ventilation, VO_2: oxygen consumption, $\Delta VO_2/\Delta WR$: the slope of the increase in VO_2 to the increase in the work rate							

Patients with Cpc-PH had a significantly lower peak $PETCO_2$ (Non-PH/Ipc-PH/Cpc-PH = 38.3 ± 6.7 vs. 35.6 ± 5.9 vs. 32.7 ± 4.0 mmHg, p = 0.006), higher VE vs. VCO_2 slope (Non-PH/Ipc-PH/Cpc-PH = 32.5 [28.2, 36.9] vs. 33.9 [29.4, 42.5] vs. 38.2 [34.1, 43.3], p = 0.043), and lower $\Delta VO_2/\Delta WR$ (Non-PH/Ipc-PH/Cpc-PH = 8.4 ± 1.5 vs. 7.7 ± 2.1 vs. 7.2 ± 1.8 mL/min/watt, p = 0.029) than those with Ipc-PH and non-PH (Fig. 2).

Predictors Of Cpc-ph Among Cpx Variables

According to the univariate logistic regression analysis, peak $PETCO_2$ (odds ratio [OR], 0.863 [95% confidence interval (CI): 0.773–0.964], p = 0.009) and $\Delta VO_2/\Delta WR$ (OR, 0.706 [95% CI: 0.503–0.990], p = 0.044) were significant predictors of Cpc-PH (Table 3). Peak $PETCO_2$ was the optimal predictor (OR, 0.854 [95% CI: 0.757–0.962], p = 0.009) in multivariate logistic regression analysis.

Table 3
Determinants of Cpc-PH.

	Univariate			Multivariate		
Variable	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
VO_2 at the AT	0.939	0.754–1.169	0.573			
Peak VO_2	0.923	0.813–1.049	0.220			
$\Delta VO_2/\Delta WR$	0.706	0.503–0.990	0.044	0.749	0.526–1.066	0.108
VE vs. VCO_2 slope	1.055	0.993–1.121	0.083			
VE/VCO_2 at the AT	1.060	0.984–1.141	0.125			
$PETCO_2$ at rest	0.968	0.825–1.067	0.334			
Peak $PETCO_2$	0.863	0.773–0.964	0.009	0.854	0.757–0.962	0.009

CI: confidence interval, AT: anaerobic threshold, $PETCO_2$: end-tidal partial pressure of carbon dioxide, VO_2: oxygen Consumption, VCO_2: carbon dioxide output, VE: minute ventilation, $\Delta VO_2/\Delta WR$: the slope of the increase in VO_2 to the increase in the work rate

Receiver operating characteristic (ROC) curve analysis revealed that peak $PETCO_2$ was an indicator of Cpc-PH with the most superior predictive value (area under the curve [AUC]: 0.747, 95% CI: 0.640–0.854, p = 0.003) (Fig. 3). Peak $PETCO_2$ < 36 mmHg showed a sensitivity of 64% and specificity of 79% in predicting Cpc-PH.

Discussion

In this study, we investigated CPX parameters in patients with non-PH, Ipc-PH, and Cpc-PH. In our cohort, 35% of the patients who underwent RHC had PH-LHD, with Cpc-PH accounting for only 13% of the entire cohort. Therefore, Cpc-PH appears to be a relatively uncommon condition, which is consistent with previous findings[18]. The present study's results also revealed that peak $PETCO_2$ was the optimal predictor of Cpc-PH, thus corroborating the findings of previous reports in which ventilatory variables proved useful in differentiating Cpc-PH[17, 18]; however, the high detection power of peak $PETCO_2$ has not been previously reported.

PH is a common complication of LHD, and it develops in response to a passive increase in left-sided filling pressures, more specifically left atrial pressure, and is associated with a poor prognosis[22]. Cpc-PH is known to have an even worse prognosis[6].

Genetically, Cpc-PH resembles PAH. Assad et al. found that patients with Cpc-PH had genetic abnormalities in pathways that were highly active in the lungs and known to contribute to the pathophysiology of PAH. These exploratory genetic findings suggest that Cpc-PH may have a pathophysiology distinct from that of Ipc-PH[3].

In pathological aspects, progressive thickening and collagen proliferation of the lamina densa occur in order to protect against fluid accumulation in the interstitium of the endothelium and vascular wall as well as in the alveoli[4, 5, 23]. In Ipc-PH, small arteries exhibit endothelial dysfunction and vasoconstriction, despite no defined changes in the composition of small pulmonary arteries, and the pulmonary veins show a certain degree of thickness and tendency toward arteriolarization. Moreover, in Cpc-PH, the venous system becomes fully arteriolarized, and the small arteries exhibit a clear muscularization process and remodeling; impairment of gas exchange diffusion or lengthening of the path between air and the red blood cells is prominent.

In an effort to differentiate Cpc-PH from Ipc-PH in a non-invasive manner, an approach based on physiology is important to detect this pathological change. In our cohort, the low peak-$PETCO_2$ value, which is one of the ventilatory variables in CPX, was an indicator of Cpc-PH with the optimal predictive value, thus potentially reflecting a marked impairment of gas exchange diffusion.

The differentiation of Cpc-PH using CPX was reported by Cariviate et al.[18]. They found VE/VCO_2 at the AT to be useful in detecting Cpc-PH, and Cpc-PH was intermediate between PAH and Ipc-PH in terms of gas exchange. Among the ventilatory parameters obtained using the submaximal exercise test, low $PETCO_2$, high VE/VCO_2, and high VD/VT were reportedly characteristic of Cpc-PH[17]. Moreover, the exacerbation of pulmonary gas exchange abnormalities in patients with Cpc-PH was related to an excessive rise in pulmonary vascular pressures[17]. Zhong et al. also reported that VE/VCO_2-related parameters were diagnostic variables for the presence of pre-capillary components in patients with PH-LHD. Among the ventilatory variables, the lowest VE/VCO_2%pred, which was obtained from the submaximal exercise test, was the optimal predictor of Cpc-PH, as demonstrated by an AUC of 0.77[24]. From our data, peak $PETCO_2$ is also particularly useful in detecting Cpc-PH, as demonstrated by an AUC of 0.75. This is comparable to that reported by Zhong et al. In the maximal exercise test, peak $PETCO_2$ was the optimal diagnostic variable.

In the HF population, the $PETCO_2$ is a known CPX variable that potentially possesses prognostic information[25]. In particular, Arena et al. reported that $PETCO_2$ change from rest to the respiratory compensation (RC) point, $PETCO_2$ at the RC point, and $PETCO_2$ at peak exercise were all significant predictors of cardiac-related events. Low $PETCO_2$ levels during exercise have classically been considered to strongly reflect low CO during exercise. Matsumoto et al. found that $PETCO_2$ at the RC point was significantly correlated with CO at peak exercise in patients with cardiac disease[26]. In addition, they concluded that decreased CO_2 production, abnormal ventilatory patterns, and compensatory

hyperventilation did not appear to explain the lower $PETCO_2$ values during exercise in patients with cardiac disease, thus further confirming lower CO as the underlying cause. Moreover, Tanabe et al. revealed a significant correlation between the $PETCO_2$ and cardiac index at peak exercise in patients with HF[27].

In patients with PAH, the $PETCO_2$ decline associated with exercise was more distinct than that in those with LHD[28]. Hemnes et al. demonstrated that the measurement of resting $PETCO_2$ at the bedside may discriminate PAH patients from those with pulmonary venous hypertension or no PH[29]. Moreover, Welch et al. also demonstrated that this readily available resting $PETCO_2$ may be a physiologically relevant marker of poor prognosis in PAH[30]. They reported that lung diffusion for carbon monoxide (DLCO) correlates with resting $PETCO_2$, suggesting that these variables could provide potentially similar insight into the degree of pulmonary vasculopathy in patients with PAH. DLCO measures the ability of a gas to diffuse from the alveoli to the red blood cells in the pulmonary capillaries and depends on alveolar–capillary membrane diffusive capacity and capillary volume, which is the amount of blood flowing through the ventilated alveolar–capillary units over a period of time, that is, a few seconds[31]. Because alveoli that are affected by dead-space ventilation have no blood flow, they are unlikely to participate in absorbing gas into the alveolar capillaries. The correlation between the $PETCO_2$ and DLCO could be explained by the fact that both are markers of dead-space ventilation. The $PETCO_2$, as well as DLCO, may also reflect capillary membrane diffusive capacity and capillary volume (i.e., CO). Peak $PETCO_2$ may better capture pathological changes in Cpc-PH whereby the venous system becomes fully arteriolarized and gas exchange is strongly impaired.

This study has certain limitations. First, our study population only included patients who were able to undergo the exercise stress test. Second, PH-LHD was classified according to the previous criteria of the 6th World Symposium on Pulmonary Hypertension in 2019. Finally, our cohort comprised a heterogeneous population of patients with cardiac disease.

In conclusion, peak $PETCO_2$ was associated with Cpc-PH in patients with LHD.

Methods

This study was conducted in accordance with relevant named guidelines and regulations as well as with the principles of the Declaration of Helsinki and was approved by the Committee for Clinical Studies and Ethics of Kyorin University School of Medicine.

Study patients

The subjects comprised 105 in-hospital consecutive patients with LHD who underwent RHC and CPX between 2012 and 2017 at our hospital. Patients with dilated cardiomyopathy (n=56), hypertrophic cardiomyopathy (n=3), secondary cardiomyopathy (n=6), ischemic cardiomyopathy (n=13), valvular heart disease (n=13), hypertensive heart disease (n=5), and diastolic dysfunction (n=9) were included. Patients

with primary right-sided HF, unstable coronary artery disease or recent revascularization, constrictive pericarditis, high-output HF, and infiltrative or restrictive cardiomyopathy were excluded.

Right heart catheterization

RHC was performed using a 6-F double-lumen balloon-tipped flow-directed Swan-Ganz catheter (Harmac Medical Products, Inc., Buffalo, NY, USA) using the transjugular approach.

Baseline hemodynamic data were recorded; the zero-reference level (mid-chest) was adjusted at the commencement of pressure measurement, and the PAWP was obtained as the mean value of the arterial trace during occlusion. Measurements were obtained at the end of a normal expiration with the patients in a resting-state supine position to assess the right chamber, RAP, right ventricular end-diastolic pressure, PAP (mean PAP, systolic PAP, and diastolic PAP), and PAWP[19]. O_2 saturation in arterial blood (SaO_2), that is, in the radial or femoral artery, and that in the pulmonary artery (SvO_2) were measured. CO was determined by the Fick method using the following formula: CO (L/min) = VO_2/(1.34 × hemoglobin × [SaO_2 – SvO_2]). PVR and diastolic pulmonary pressure gradient (DPG) were calculated as follows: PVR (WU) = (mean PAP – PAWP)/CO and DPG = diastolic PAP – PAWP, respectively.

Hemodynamic definition

To investigate hemodynamics according to the presence of pulmonary vasculopathy, we divided patients into the following PH subgroups according to recommendations published in the 2015 ESC/ERS guidelines: (i) non-PH (mean PAP <25 mmHg), (ii) Ipc-PH (mean PAP ≥25 mmHg with PVR ≤3.0 WU and/or DPG <7 mmHg), and (iii) Cpc-PH (mean PAP ≥25 mmHg with PVR >3.0 WU and/or DPG ≥7 mmHg)[2].

Cardiopulmonary exercise testing

An incremental symptom-limited exercise test was performed within 3 weeks of RHC using an electromagnetically braked cycle ergometer (Strength Ergo 8, Fukuda Denshi, Tokyo, Japan) according to the ramp protocol. The test comprised a 3-min resting period, followed by 3 min of warm-up at an ergometer setting of 10 W (60 rpm) and subsequent testing involving a 1–2-W increase in exercise load every 6 s (10–20 W/min), depending on the predicted maximum exercise capacity, such that maximal effort was attained within 8–15 min. Heart rate, arterial blood pressure recorded in the brachial artery, and the electrocardiogram were monitored continuously during the test.

During exercise, oxygen consumption (VO_2), carbon dioxide output (VCO_2), and minute ventilation (VE) were measured using a metabolic cart (AE-302S; MINATO, Tokyo, Japan). Prior to calculating the parameters from respiratory gas analysis, an eight-point moving average of the breath-by-breath data was obtained. Peak VO_2 was defined as the average value obtained during the last 30 s. The AT point was determined using the *V*-slope method in addition to the following conventional criteria: VE/VO_2 increases after registering as flat or decreasing, whereas VE/VCO_2 remains constant or decreases[20,21].

The VE vs. VCO_2 slope was calculated from the commencement of incremental exercise to the RC point using least squares linear regression[12]. The $PETCO_2$ was recorded at rest, AT, and peak exercise. The slope of VO_2 increase to work-rate increase ($\Delta VO_2/\Delta WR$), reflecting the rate of CO increase, was calculated from the data recorded between 30 s after the commencement of incremental exercise to 30 s before the end of the exercise using least squares linear regression.

Echocardiography

Transthoracic Doppler echocardiography was performed, and echocardiograms were stored digitally on an ATRADA (Cannon, Japan) ultrasound system. The frame rate was maintained at a minimum rate of 60/s. For Doppler recordings, an average of 3–5 consecutive beats were measured using a horizontal sweep of 75–100 cm/s. The left ventricular (LV) volumes and LVEF were measured using the biplane Simpson method. The LV internal diameter and the septal and posterior wall thicknesses were measured at the end of diastole.

Statistical analysis

Analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test and analysis of histograms were performed to assess normality. Continuous variables are presented as mean±SD or median (25^{th}, 75^{th} interquartile range), where appropriate. Comparisons of more than two groups were performed using one-way analysis of variance (with the Turkey post-hoc test) or the Kruskal–Wallis (with Dunn's post-hoc test) test, where appropriate. Categorical variables are presented as percentages and were compared using Fisher's exact test or Pearson's χ^2 test. Univariate logistic regression analysis was performed to predict Cpc-PH using CPX parameters. In multivariate logistic regression analysis, variables that were significant in the univariate analysis were selected. ROC curves were constructed, and the AUC was calculated. The cutoff value resulting in the highest product of sensitivity and specificity was considered optimal for the detection of Cpc-PH. Statistical significance was set at $p<0.05$.

Declarations

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Author contributions

A.G designed the study, analyzed the data, and wrote the manuscript. T.K, T.S, and K.S reviewed the data and edited the manuscript. Y.Y, S.T, K.T, H.K, T.I, and A.G performed the RHC and exercise tests.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no potential conflict of interest related to any company or organization whose products or services are discussed in this article.

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Figures

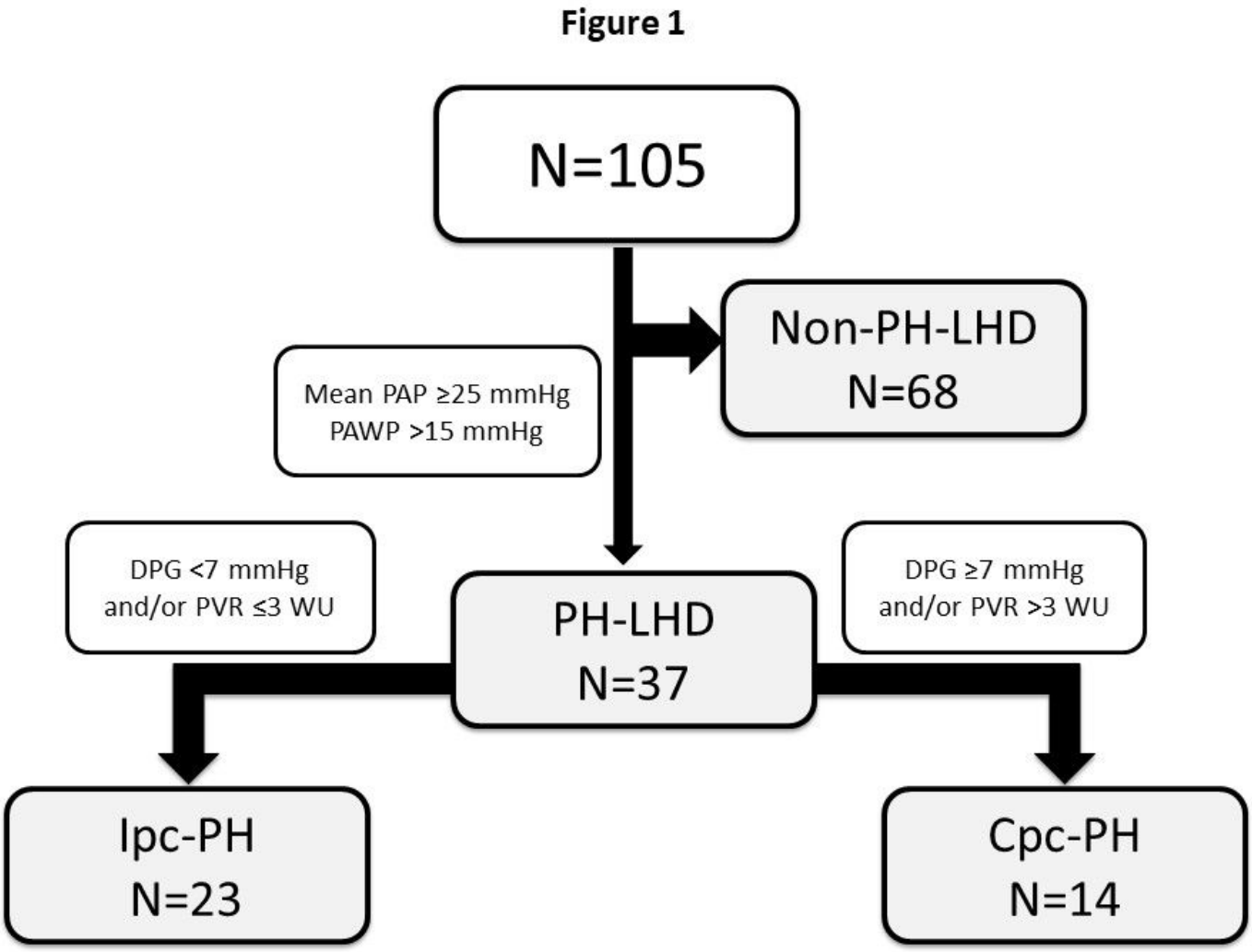

Figure 1

Flowchart of patients with left heart disease who underwent cardiopulmonary exercise testing and right heart catheterization. Cpc: combined post-capillary and pre-capillary, DPG: diastolic pressure gradient, Ipc:

isolated post-capillary, LHD: left heart disease, PAP: pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, PH: pulmonary hypertension, PVR: pulmonary vascular resistance.

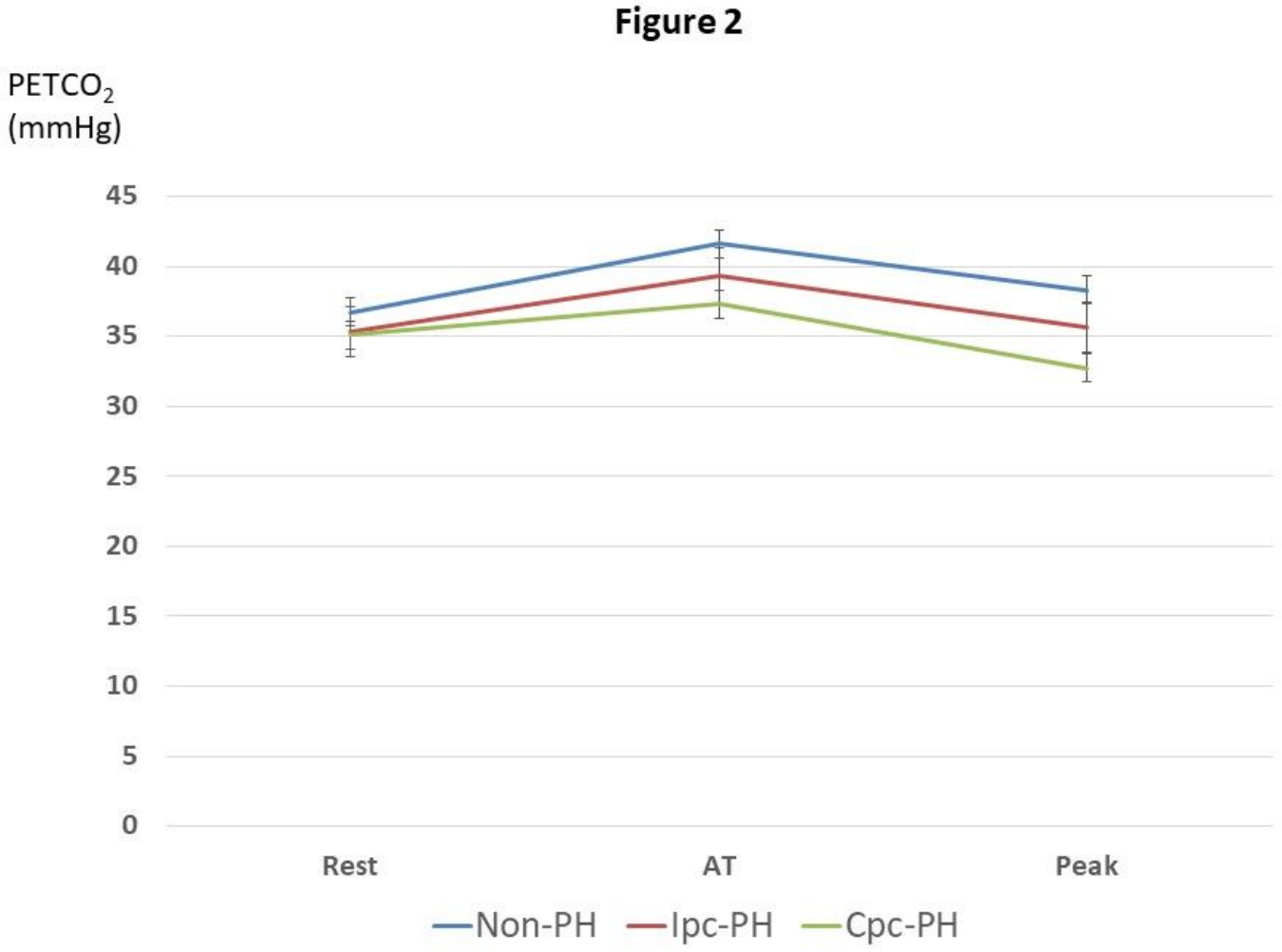

Figure 2

Evolution of $PETCO_2$ from rest to peak exercise in the three groups of patients. AT: anaerobic threshold, $PETCO_2$: end-tidal partial pressure of carbon dioxide.

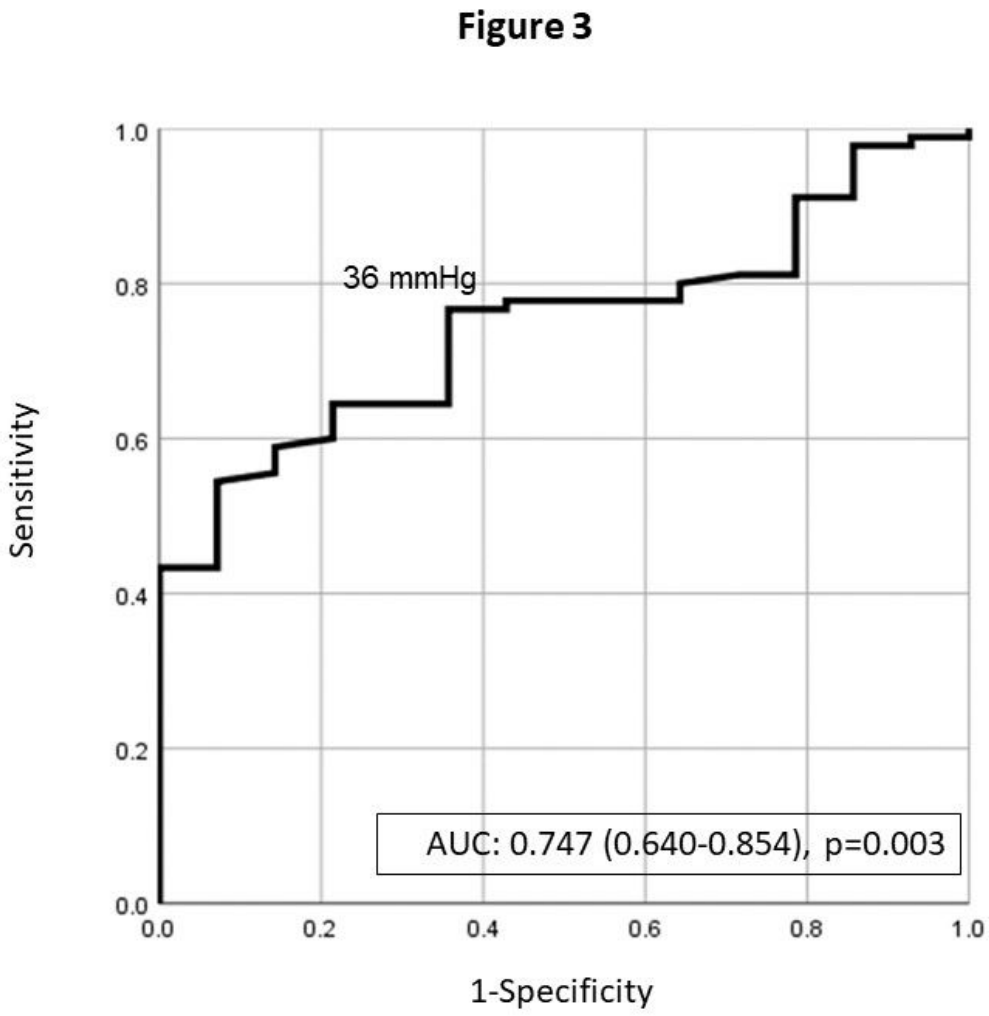

Figure 3

Receiver operating characteristic curves for peak $PETCO_2$ to detect Cpc-PH. AUC: area under the curve, $PETCO_2$: end-tidal partial pressure of carbon dioxide