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Usefulness of ventilatory gas analysis for the non-invasive evaluation of the severity of chronic thromboembolic pulmonary hypertension

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ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by organic thrombotic obstructions in the pulmonary arteries with reduced pulmonary vascular reserve. This study aimed to examine whether postural changes in ventilatory gas analysis parameters are useful for assessing pulmonary hemodynamics in patients with CTEPH.

Methods: A total of 44 patients with newly diagnosed CTEPH (CTEPH group), 33 patients with improved CTEPH (mean pulmonary arterial pressure [mPAP] <25 mm Hg), and 25 controls were enrolled. Patients with improved CTEPH referred to patients without residual PH who were previously diagnosed with CTEPH and already received optimal therapies. Various pulmonary function parameters were examined in supine and sitting positions, and postural changes were calculated (Δ[supine − sitting]). In 32 patients with CTEPH, we examined hemodynamic and ventilatory gas analysis parameters before the first balloon pulmonary angioplasty (BPA) and during follow-up.

Results: Patients with CTEPH had significantly lower supine end-tidal carbon dioxide pressure ($P_{ET}CO_2$) and $\Delta P_{ET}CO_2$ than controls (both $P < 0.001$), and these parameters were significantly correlated with mPAP ($R^2 = 0.507$, $P < 0.0001$ and $R^2 = 0.470$, $P < 0.001$, respectively). Supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were significantly lower in patients with improved CTEPH than in controls (both $P < 0.001$). Hemodynamic and echocardiographic parameters were comparable in both groups. Furthermore, significant correlation between the change in mPAP and change in supine $P_{ET}CO_2$ by BPA was noted ($R^2 = 0.478$, $P < 0.001$).

Conclusion: These results indicate that postural changes in ventilatory gas analysis parameters are useful and non-invasive method for the evaluation of mPAP, which is one of the hemodynamic parameters of CTEPH severity.

1. Introduction

Pulmonary hypertension (PH) has a poor prognosis owing to increased pulmonary arterial pressure (PAP), resulting in progressive right heart failure [1–3]. Chronic thromboembolic pulmonary hypertension (CTEPH) is a type of PH characterized by organic thrombotic obstructions in the pulmonary arteries with reduced pulmonary vascular reserve [4]. Recently, balloon pulmonary angioplasty (BPA) has been reported to improve long-term prognosis and respiratory function in patients with inoperable CTEPH [5–7].

Right heart catheterization (RHC) remains the gold standard for diagnosing PH and assessing disease severity and response to therapy. However, RHC is invasive and carries a small but well-defined risk; furthermore, repeated RHC for follow-up imposes a heavy burden on patients [8,9]. Despite being a non-invasive tool for the screening and follow-up of patients with CTEPH, echocardiography may underestimate PAP in mild PH and is unable to detect PH in the early stages [10,11]. Moreover, an increase in resting PAP is a late marker of pulmonary vascular disease (PVD) because approximately 50% of the pulmonary circulation is already obstructed before an increase in resting PAP is detected [12–15].

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However, many current screening modalities depend on the detection of PAP elevation and thus fail to identify a mild increase in PAP at an early stage of PH. Hence, non-invasive methods for the assessment of slight change in the pulmonary circulation and PVD remain to be developed.

Postural change from sitting to supine position is known to improve the ventilation/perfusion mismatch because of pulmonary perfusion redistribution, reflecting the presence of functional pulmonary vascular reserve [16]. Moreover, a decrease in pulmonary vascular reserve leads to an attenuation of pulmonary perfusion redistribution [4]. When perfusion redistribution was quantified using single-photon emission computed tomography/computed tomography (SPECT/CT) perfusion imaging, the quantification of the degree of perfusion redistribution with postural change was useful for assessing the functional vascular reserve of the pulmonary circulation and correlated with PH severity, such as mean PAP (mPAP), 6-min walk distance, and the World Health Organization functional class [17]. Moreover, end-tidal carbon dioxide pressure ($P_{ET}CO_2$) as a non-invasive parameter in ventilatory gas analysis reflects pulmonary blood flow and ventilation/perfusion mismatch [18,19].

Thus, combining measures of postural changes in ventilatory gas analysis parameters could be a non-invasive and simple method for the assessment of mPAP, which is one of the parameters of CTEPH severity. To develop a non-invasive method for the evaluation of the degree of mPAP, the present study aimed to examine whether postural changes in ventilatory gas analysis parameters are useful for assessing pulmonary hemodynamics in patients with CTEPH.

2. Methods

2.1. Study subjects

A total of 44 patients with newly diagnosed CTEPH (CTEPH group), 33 patients with improved CTEPH (mPAP <25 mm Hg after receiving optimal therapies including vasodilator therapy and surgical therapies, BPA, or both), and 25 controls were enrolled from September 2015 to October 2018. Patients with improved CTEPH referred to patients without residual PH who were previously diagnosed with CTEPH and already received optimal therapies, including vasodilator therapy and surgical therapies, BPA, or both. A diagnosis of CTEPH was established based on published clinical guidelines [3]. Controls pertained to those with suspected PH but normal mPAP values. Patients with other associated forms of PH, a constant need for supplemental oxygen (O_2), or O_2 saturation of <85% in ambient air were excluded from the analysis. We performed RHC, echocardiography, and ventilatory gas analysis with patients in sitting and supine positions within 3 days before or after RHC.

2.2. RHC

All patients underwent RHC with a 6-Fr Swan–Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) in the supine position. Pulmonary vascular resistance, mPAP, cardiac output (CO), cardiac index (CI), stroke volume (SV), and stroke volume index (SVI) were measured, with the CO and SV being determined using the indirect Fick method. CI and SVI were calculated by dividing the CO and SV by the body surface area. To calculate intrapulmonary shunt, we measured O_2 saturation/partial pressure (PaO_2) in the artery and pulmonary artery, and blood gas analyses were performed using arterial and pulmonary arterial blood samples obtained during RHC in room air. Moreover, the shunt was calculated using the following standard formula [20]:

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$$

where Qs represents the shunt flow; Qt, the systemic blood flow; CcO_2, the pulmonary capillary O_2 content; CaO_2, the arterial O_2 content; and CvO_2, the mixed venous O_2 content.

$$CcO_2 - CaO_2 = Hb \times 1.36\ (1 - SaO_2) + 0.0031\ (P_AO_2 - PaO_2)$$

$$CcO_2 - CaO_2 = Hb \times 1.36\ (1 - SvO_2) + 0.0031\ (P_AO_2 - P_VO_2)$$

where Hb refers to hemoglobin (g/dL); SaO_2, arterial O_2 saturation; SvO_2, mixed venous O_2 saturation; P_AO_2, alveolar O_2 partial pressure; PaO_2, arterial O_2 partial pressure; and PvO_2, mixed venous O_2 partial pressure.

2.3. BPA

We performed a total of 127 BPA procedures (mean, 4.0 ± 0.4 procedures per patient) in 32 patients with newly diagnosed CTEPH (distal type and inoperable). All patients with CTEPH who underwent BPA were included in the CTEPH group prior to BPA. BPA was performed through the right femoral vein to treat the pulmonary arterial branches [5]. Targeted vessels were selected based on comprehensive findings, including webs, bands, abrupt narrowing, and complete obstructions, as well as those derived from angiography, 3D-reconstructed computed tomography, and intravascular imaging modalities such as optical coherence computed tomography. The BPA procedure was limited to a maximum of three lobes per procedure and was repeated at an interval of 4–8 weeks in all patients. BPA was repeated until mPAP became <30 mm Hg.

2.4. Ventilatory gas analysis

Ventilatory gas analysis was performed using an expired gas analyzer (AE-100i; Minato Medical Science, Osaka, Japan) with patients in sitting and supine positions. Ventilatory gas analysis parameters such as minute ventilation (VE), tidal volume (VT), respiratory rate, O_2 uptake, carbon dioxide output (VCO_2), and $P_{ET}CO_2$ were continuously measured in all subjects using a breath-by-breath method. From these data, derived variables, including VE/VCO_2 and the physiological dead space to VT ratio, were calculated.

Patients wore the mask, and data were recorded in the sitting position for 5 min and subsequently in the supine position for another 5 min. Expiratory gas analysis was performed during the last 1 min at each position. Patients were instructed to maintain normal tidal breathing during the analysis. Differences in various ventilatory gas analysis parameters between sitting and supine positions were defined as follows: (Δ[supine − sitting]).

2.5. Echocardiography

Study subjects underwent standard echocardiographic examination in accordance with the recommendations by the American Society of Echocardiography and the European Association of Echocardiography [21,22]. In addition, echocardiographic parameters such as ejection fraction, right ventricular fractional area change, tricuspid regurgitation pressure gradient, and tricuspid annular plane systolic excursion were measured.

2.6. Informed consent

All patients provided informed consent for their participation in the study. The study was conducted in accordance with the Declaration of Helsinki principles, and the study protocol (no. 2016-1-254) was approved by the ethics committee of Tohoku University Graduate School of Medicine.

2.7. Statistical analyses

Results are expressed as means ± standard deviation. Statistical analysis was performed using SPSS version 21 (IBM Corp., Armonk, NY, USA). Comparisons between groups were performed using one-way analysis of variance. Postural changes in ventilatory gas analysis parameters were examined using repeated-measures analysis of variance with postural change as a within-subject effect and group as a between-subject effect. The Bonferroni test was used for post hoc analysis when significant differences were detected. The association between hemodynamic and ventilatory gas analysis parameters was evaluated using Spearman's correlation. A two-sided *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline subject characteristics

Baseline subject characteristics are summarized in Table 1. The control group comprised patients with dyspnea and abnormal echocardiographic parameters. Some patients had connective tissue disease ($n = 13/25$) and pulmonary embolism ($n = 2/25$). Hemodynamic and echocardiographic parameters in the control and improved CTEPH groups were comparable, whereas only the CI was significantly lower in the improved CTEPH group. The intrapulmonary shunt value significantly differed among the three groups. Furthermore, in ventilatory gas analysis, $P_{ET}CO_2$ in sitting and supine positions significantly differed among the three groups (Table 1).

3.2. Changes in ventilatory gas analysis parameters between sitting and supine positions

In the CTEPH group, $P_{ET}CO_2$ significantly decreased with postural change ($P < 0.001$). In contrast, $P_{ET}CO_2$ increased with postural change in the control and improved CTEPH groups ($P < 0.001$ and $P = 0.007$, respectively). There was a statistically

significant interaction with postural change in $P_{ET}CO_2$ among the three groups (interaction, $P < 0.001$). VE/VCO_2 significantly increased with postural change in the CTEPH group ($P < 0.001$) but significantly decreased in the control group ($P < 0.001$).

3.3. Postural change in ventilatory gas analysis parameters in the improved CTEPH and control groups

$\Delta P_{ET}CO_2$ and $\Delta VE/VCO_2$ significantly differed among the three groups (Fig. S1). Moreover, the improved CTEPH group had significantly lower $\Delta P_{ET}CO_2$ and significantly higher $\Delta VE/VCO_2$ than the control group ($P < 0.001$ and $P = 0.007$, respectively), although no differences in hemodynamic and echocardiographic parameters or respiratory functions were noted between the two groups (Table 1).

Table 1
Baseline characteristics of enrolled patients.

Characteristic	Control ($n = 25$)	Improved CTEPH ($n = 33$)	CTEPH ($n = 44$)
Female:male (n)	23:2	27:6	35:9
Age (years)	62.3 ± 16.0	65.3 ± 11.3	67.2 ± 12.4
mPAP (mmHg)	18.0 ± 3.5	20.0 ± 3.1	38.1 ± 9.3**,§
PVR (dyne·s·cm^{-5})	155 ± 56	229 ± 86	702 ± 306**,§
CO (mL/min)	4.05 ± 1.10	3.75 ± 1.03	3.29 ± 0.98*
CI (L/min/m^2)	2.76 ± 0.68	2.33 ± 0.51*	2.16 ± 0.54**
SvO_2 (%)	71.7 ± 5.1	68.1 ± 3.7	61.2 ± 7.2**,§
PvO_2 (mmHg)	40.6 ± 3.4	37.2 ± 2.3**	34.2 ± 3.5**,§
SaO_2 (%)	95.8 ± 2.4	93.5 ± 3.3	88.5 ± 4.6**,§
PaO_2 (mmHg)	86.0 ± 11.6	70.1 ± 10.7**	56.7 ± 10.0**,§
$PaCO_2$ (mmHg)	39.6 ± 3.0	40.3 ± 3.7	36.0 ± 5.1**,§
Shunt (%)	15.1 ± 7.9	21.2 ± 9.3*	30.6 ± 9.3**,§
EF (%)	64.2 ± 12.6	67.3 ± 5.9	69.5 ± 7.8
RVFAC (%)	42.2 ± 8.3	41.7 ± 8.2	27.4 ± 8.8**,§
TAPSE (mm)	21.3 ± 4.5	21.0 ± 2.8	18.1 ± 3.9**,‡
TRPG (mmHg)	33.6 ± 11.9	34.9 ± 15.3	69.6 ± 27.9**,§
%DLco	83.2 ± 24.5	84.1 ± 16.6	92.6 ± 22.6
6MWD (m)	521 ± 97	509 ± 96	377 ± 134**,§
Sitting VE (L/min)	8.7 ± 1.8	9.4 ± 2.0	10.4 ± 1.8**
Supine VE (L/min)	8.3 ± 2.0	9.0 ± 1.8	10.4 ± 1.8**,§
Sitting RR (f/min)	17.9 ± 4.7	16.6 ± 4.0	15.9 ± 4.3
Supine RR (f/min)	15.1 ± 4.1	15.7 ± 5.0	16.6 ± 4.9
Sitting VD/VT	0.40 ± 0.05	0.36 ± 0.05*	0.37 ± 0.05
Supine VD/VT	0.38 ± 0.06	0.35 ± 0.06	0.37 ± 0.06
Sitting $P_{ET}CO_2$ (mmHg)	35.2 ± 3.1	33.0 ± 3.1*	29.5 ± 2.9**,§
Supine $P_{ET}CO_2$ (mmHg)	37.5 ± 3.4	33.8 ± 3.6**	28.1 ± 3.0**,§
Sitting VE/VCO_2	49.2 ± 9.3	46.8 ± 5.0	54.2 ± 7.8*,§
Supine VE/VCO_2	43.2 ± 8.3	44.1 ± 10.5	57.6 ± 9.3**,§
Targeted treatments for PH			
PEA		1/33 (3.0%)	
BPA		27/33 (81.8%)	
Medication		14/33 (42.4%)	
Monotherapy		7/33 (21.2%)	
Dual therapy		3/33 (9.1%)	
Triple therapy		4/33 (12.1%)	

Values are mean ± SD.
6MWD = 6-min walk distance; BPA = balloon pulmonary angioplasty; CI = cardiac index; CO = cardiac output; CTEPH = chronic thromboembolic pulmonary hypertension; DLco = diffusing capacity of the lung for carbon monoxide; EF = ejection fraction; mPAP = mean pulmonary arterial pressure; $PaCO_2$ = arterial CO_2 partial pressure; PaO_2 = arterial O_2 partial pressure; PEA = pulmonary endarterectomy; $P_{ET}CO_2$ = end-tidal CO_2 pressure; PvO_2 = mixed venous O_2 partial pressure; PVR = pulmonary vascular resistance; RR = respiratory rate; RVFAC = right ventricular fractional area change; SaO_2 = arterial O_2 saturation; SvO_2 = mixed venous O_2 saturation; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid regurgitation pressure gradient; VD/VT = physiological dead space to tidal volume ratio; VE = minute ventilation; VE/VCO_2 = ventilation to carbon dioxide production ratio.
* $P < 0.05$ vs. control group.
** $P < 0.01$ vs. control group.
‡ $P < 0.05$ vs. improved CTEPH group.
§ $P < 0.01$ vs. improved CTEPH group.

3.4. Correlation between ventilatory gas analysis and hemodynamic parameters

Supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were significantly correlated with mPAP in all study subjects ($R^2 = 0.507$, $P < 0.001$ and $R^2 = 0.470$, $P < 0.001$, respectively) (Fig. 1). Supine VE/VCO_2 and $\Delta VE/VCO_2$ were significantly correlated with mPAP ($R^2 = 0.314$, $P < 0.001$ and $R^2 = 0.214$, $P < 0.001$, respectively).

To consider the effect of intrapulmonary shunt, the correlations between intrapulmonary shunt and ventilatory gas analysis/hemodynamic parameters were examined. Supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were correlated with intrapulmonary shunt ($R^2 = 0.197$, $P < 0.001$ and $R^2 = 0.270$, $P < 0.001$, respectively). In addition, intrapulmonary shunt was significantly correlated with mPAP ($R^2 = 0.292$, $P < 0.001$).

3.5. Change in ventilatory gas analysis and hemodynamic parameters by BPA

We examined hemodynamic and ventilatory gas analysis parameters before the first BPA and during follow-up (40 ± 18 weeks after the first BPA, $n = 32$) (Table 2). mPAP significantly decreased after BPA ($P < 0.001$). CI was unchanged after BPA ($P = 0.794$). After BPA, the heart rate was significantly decreased ($P < 0.001$), resulting in a significant increase in SVI after BPA ($P = 0.044$) (Table 2). %DLco significantly decreased after BPA ($P = 0.018$).

Supine $P_{ET}CO_2$ significantly increased after BPA ($P < 0.001$). Furthermore, a significant correlation between the change in mPAP and change in supine $P_{ET}CO_2$ was noted ($R^2 = 0.478$, $P < 0.001$) (Fig. 2).

4. Discussion

The novel findings of the present study are as follows: (1) supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were significantly different among the three groups; (2) supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were associated with mPAP; and (3) the improvement in mPAP was significantly correlated with the change in supine $P_{ET}CO_2$ among patients with CTEPH who underwent BPA. To the best of our knowledge, this study is the first to show that ventilatory gas analysis in different positions is useful for the evaluation of mPAP, which is one of the parameters of CTEPH severity.

4.1. Effect of postural change on ventilatory gas analysis parameters in patients with CTEPH

Postural change from sitting to supine position usually improves ventilation/perfusion mismatch because of the presence of pulmonary vascular reserve and increased functional pulmonary blood flow in healthy subjects [23–25]. These changes lead to an increase in $P_{ET}CO_2$ and a decrease in VE/VCO_2. Thus, postural change from sitting to supine position significantly decreased VE/VCO_2 and increased $P_{ET}CO_2$ in the control group.

Conversely, in patients with CTEPH, we demonstrated that $P_{ET}CO_2$ significantly decreased with postural change ($P < 0.001$). In the CTEPH group, pulmonary vascular reserve was reduced, and it did not result in posture-induced improvement in ventilation/perfusion mismatch. Moreover, patients with CTEPH are known to have intrapulmonary shunts, in which shunt flow via a pre-existing arteriovenous anastomosis is increased by elevated PAP [26,27]. The effects of intrapulmonary shunts on pulmonary circulation and gas exchange are made apparent by postural change, particularly in the supine position [28]. In addition, the presence of intrapulmonary shunts leads to lower $P_{ET}CO_2$ and higher VE/VCO_2 values [29]. Therefore, the reduction in $P_{ET}CO_2$ with the change in

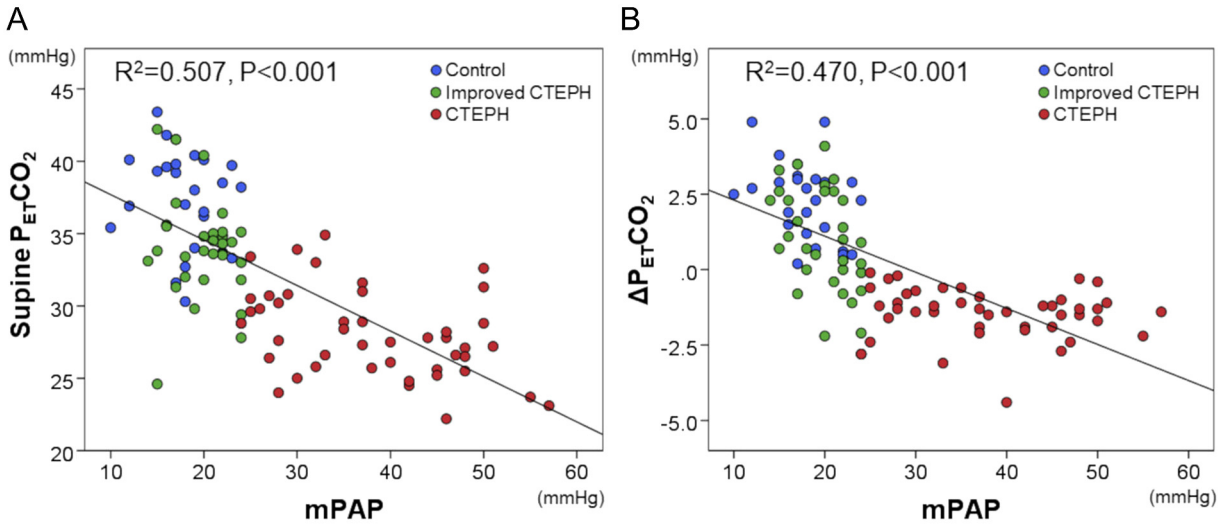

Fig. 1. Correlation between ventilatory gas analysis and hemodynamic parameters. (A) Supine $P_{ET}CO_2$ and mPAP, (B) $\Delta P_{ET}CO_2$ and mPAP. mPAP = mean pulmonary arterial pressure; $P_{ET}CO_2$ = end-tidal CO_2 pressure.

position from sitting to supine in the CTEPH group may be partially explained by mechanisms that increase shunt flow in response to postural change.

Our most notable finding was that postural change in supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ was significantly different among the three study groups. In particular, supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were significantly lower in the improved CTEPH group than in the control group, whereas the hemodynamic and echocardiographic parameters and respiratory functions were comparable between these groups (Table 1, Fig. S1). Moreover, supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ were associated with mPAP (Fig. 1). These findings suggest that mild abnormalities in the pulmonary circulation can be possibly detected using ventilatory gas analysis with postural change and that low supine $P_{ET}CO_2$ and $\Delta P_{ET}CO_2$ may be more useful, sensitive, and non-invasive markers for the evaluation of mPAP.

Table 2
Patient characteristics before balloon pulmonary angioplasty and during follow-up.

Characteristic	Before BPA (n = 32)	During follow-up (n = 32)	P-value
mPAP (mm Hg)	36.5 ± 8.8	23.2 ± 4.3	<0.001
PVR (dyne s cm^{-5})	692 ± 290	328 ± 149	<0.001
CO (mL/min)	3.55 ± 1.03	3.51 ± 0.89	0.839
CI (L/min/m^2)	2.38 ± 0.63	2.35 ± 0.45	0.794
Heart rate (/min)	71.3 ± 10.7	62.3 ± 9.0	<0.001
SV (mL/min/m^2)	51.2 ± 15.7	56.8 ± 15.2	0.011
SVI (mL/m^2)	34.5 ± 9.7	37.6 ± 7.4	0.044
SvO_2 (%)	62.1 ± 6.8	66.2 ± 7.2	0.001
PvO_2 (mm Hg)	34.4 ± 3.0	37.0 ± 3.2	<0.001
SaO_2 (%)	88.8 ± 4.5	93.4 ± 3.2	<0.001
PaO_2 (mm Hg)	57.9 ± 9.2	71.0 ± 10.8	<0.001
$PaCO_2$ (mm Hg)	35.8 ± 3.4	39.2 ± 4.6	<0.001
Shunt (%)	30.3 ± 9.2	20.3 ± 8.0	<0.001
EF (%)	69.5 ± 7.8	68.7 ± 6.0	0.700
RVFAC (%)	25.7 ± 10.3	35.7 ± 7.9	<0.001
TAPSE (mm)	18.9 ± 4.9	21.4 ± 3.6	0.063
TRPG (mm Hg)	74.8 ± 32.8	37.3 ± 18.8	<0.001
%DLco	91.3 ± 15.5	85.0 ± 16.1	0.018
Sitting $P_{ET}CO_2$ (mm Hg)	30.5 ± 3.0	33.8 ± 2.3	<0.001
Supine $P_{ET}CO_2$ (mm Hg)	29.2 ± 3.2	34.2 ± 2.6	<0.001
Sitting VE/VCO_2	53.7 ± 9.1	47.0 ± 6.4	<0.001
Supine VE/VCO_2	56.8 ± 12.4	46.1 ± 6.8	<0.001
6MWD (m)	412 ± 105	503 ± 96	<0.001

Values are mean ± SD.
6MWD = 6-min walk distance; BPA = balloon pulmonary angioplasty; CI = cardiac index; CO = cardiac output; DLco = diffusing capacity of the lung for carbon monoxide; EF = ejection fraction; mPAP = mean pulmonary arterial pressure; $PaCO_2$ = arterial CO_2 partial pressure; PaO_2 = arterial O_2 partial pressure; $P_{ET}CO_2$ = end-tidal CO_2 pressure; PvO_2 = mixed venous O_2 partial pressure; PVR = pulmonary vascular resistance; RVFAC = right ventricular fractional area change; SaO_2 = arterial O_2 saturation; SV = stroke volume; SVI = stroke volume index; SvO_2 = mixed venous O_2 saturation; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid regurgitation pressure gradient; VE/VCO_2 = ventilation to carbon dioxide production ratio.

4.2. Changes in hemodynamics and ventilatory gas analysis parameters with BPA

As shown in Fig. 2, the improvement in mPAP by BPA paralleled the improvement in supine $P_{ET}CO_2$. Thus, supine $P_{ET}CO_2$ may be a more useful parameter for the assessment of responses to treatment in patients with CTEPH. In this study, intrapulmonary shunts significantly decreased after BPA ($P < 0.001$) (Table 2). Therefore, supine $P_{ET}CO_2$ was considered to reflect a decrease in intrapulmonary shunts which leads to lower $P_{ET}CO_2$ and higher VE/VCO_2

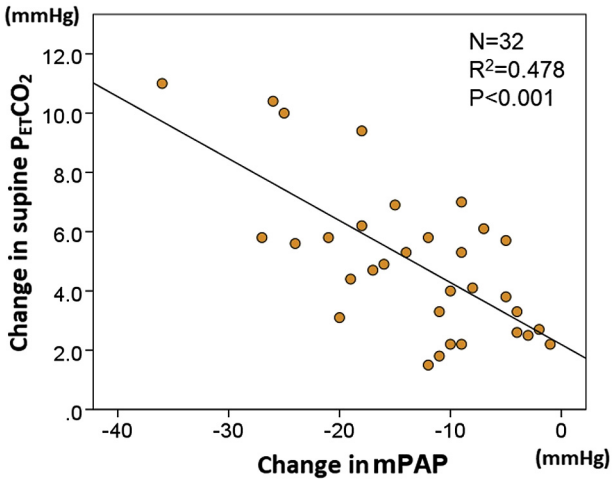

Fig. 2. Correlation between change in supine $P_{ET}CO_2$ and change in mPAP. mPAP = mean pulmonary arterial pressure; $P_{ET}CO_2$ = end-tidal CO_2 pressure.

values with the improvement of the mPAP by BPA. Thus, supine $P_{ET}CO_2$ was a useful non-invasive parameter to evaluate the degree of change in mPAP by BPA.

Although CI was unchanged after BPA, the decrease in heart rate after BPA induced a significant increase in SVI (Table 2). Aoki et al. reported that the reduction in heart rate induced by hemodynamic improvement may be associated with a reduction in CI after BPA [5]. Thus, the reduction in heart rate induced by hemodynamic improvement in this study may also be associated with no change in CI after BPA. However, no evidence on such theory about the change in CI has been reported; thus, further studies are required to reveal the mechanisms involved.

Interestingly, the %DLco significantly decreased after BPA (Table 2). This might be explained by the intrapulmonary shunt effect. CTEPH is characterized by organic thrombotic obstructions of the pulmonary arteries, which increase V/Q mismatch. However, as pulmonary capillary blood volume is maintained by a compensatory blood flow increase to the non-occluded pulmonary artery (increased blood flow and intra-pulmonary shunt), the DLco might be near normal before BPA. Indeed, it has been reported that DLco is often within the normal range in CTEPH patients [30]. An intrapulmonary shunt could contribute to the hypoxemia seen in CTEPH [27,31]. Furthermore, BPA improves oxygenation through a decrease in intra-pulmonary shunt [26]. In the present study, the intrapulmonary shunt was significantly decreased after BPA, and SaO_2 and PaO_2 were significantly improved after BPA (Table 2). Regarding the decrease of %DLco, it has been reported that the % DLco remained unchanged or slightly decreased even after extensive reperfusion with BPA or PEA [26,32]. In summary, due to the effect of an intrapulmonary shunt, it is considered that %DLco showed normal values due to compensatory blood flow increase to the non-occluded pulmonary artery before BPA, and the decrease in the %DLco was as a result of the intrapulmonary shunt after BPA with hemodynamic improvements.

4.3. Usefulness of ventilatory gas analysis with postural change as a non-invasive method

A previous study has shown that cardiopulmonary exercise testing for exercise stress using ventilator gas analysis is a useful diagnostic tool for the detection of CTEPH in patients with suspected PH in whom echocardiography findings reveal no abnormalities [33]. However, exercise tests may occasionally add more load than that expected by clinicians in critically ill patients with PH.

In this study, the postural change method is simple, safe, and feasible in clinical practice. Thus, $\Delta P_{ET}CO_2$ and supine $P_{ET}CO_2$ may be useful as surrogate markers of mPAP, which is one of the parameters of CTEPH severity, particularly during follow-up. Evidently, RHC remains an essential tool for the diagnosis and assessment of PH. However, this method may potentially diminish the frequency of RHC for the management of CTEPH.

4.4. Study limitations

The present study has several limitations. First, it is a single-center study that included a relatively small number of patients. Thus, the present findings need to be confirmed by future multicenter studies with a large sample size. Second, our control group did not comprise healthy individuals. All 25 patients belonging to the control group had dyspnea, whereas some presented with abnormal echocardiographic parameters. However, in all control subjects, mPAP was under the hemodynamic definition of PH. Therefore, showing the differences between patients with CTEPH and controls with suspected PH is of even greater value. Third, we did not measure CO using the direct Fick method in the present study. As reported, the indirect Fick method is an acceptable method but lacks reliability [3]. Thus, the indirect Fick method might have affected our value of CO. However, in this study, PAP was directly measured. Therefore, measurement of CO with the indirect Fick method is independent of our findings demonstrating a correlation between mPAP, one of the parameters of CTEPH severity and $P_{ET}CO_2$ in this study, and $P_{ET}CO_2$ before and after treatment. Finally, in the present study, treatments for improved CTEPH were not unified, including surgical therapies, BPA, or both and vasodilator therapy. These differences in therapies might have affected ventilatory parameter measurements.

5. Conclusions

Ventilatory gas analysis in different positions is a useful and non-invasive method for the evaluation of mPAP, which is one of the hemodynamic parameters of CTEPH severity. This novel method may have important clinical applications such as evaluation of serial changes related to the clinical course or therapeutic interventions in patients with CTEPH.

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Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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