Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Non-invasive screening using ventilatory gas analysis to distinguish between chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension

MINA AKIZUKI,[1] KOICHIRO SUGIMURA,[2] TATSUO AOKI,[2] TAKAAKI KAKIHANA,[1] SHUNSUKE TATEBE,[2] SAORI YAMAMOTO,[2] HARUKA SATO,[2] KIMIO SATOH,[2] HIROAKI SHIMOKAWA[2] AND MASAHIRO KOHZUKI[1]

[1]*Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan;* [2]*Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*

ABSTRACT

Background and objective: **Clinical presentations associated with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) at rest are highly similar. Differentiating between CTEPH and PAH using non-invasive techniques remains challenging. Thus, we examined whether analysis of ventilatory gas in response to postural changes can be useful as a non-invasive screening method for pulmonary hypertension (PH), and help differentiate CTEPH from PAH.**

Methods: **We prospectively enrolled 90 patients with suspected PH and performed right heart catheterization, ventilation/perfusion scan and ventilatory gas analysis. Various pulmonary function parameters were examined in the supine and sitting postures, and postural changes were calculated (Δ(supine − sitting)).**

Results: **In total, 25 patients with newly diagnosed PAH, 40 patients with newly diagnosed CTEPH and 25 non-PH patients were included. ΔEnd-tidal CO_2 pressure ($P_{ET}CO_2$) was significantly lower in patients with CTEPH and PAH than in non-PH patients (both $P < 0.001$). $\Delta P_{ET}CO_2 < 0$ mm Hg could effectively differentiate PH from non-PH (area under the curve (AUC) = 0.969, sensitivity = 89%, specificity = 100%). Postural change from sitting to supine significantly increased the ratio of ventilation to CO_2 production (VE/VCO_2) in the CTEPH group ($P < 0.001$). By contrast, VE/VCO_2 significantly decreased in the PAH group ($P = 0.001$). Notably, CTEPH presented with higher $\Delta VE/VCO_2$ than PAH, although no differences were observed in haemodynamic and echocardiographic parameters between the two groups ($P < 0.001$). Furthermore, $\Delta VE/VCO_2 > 0.8$ could effectively differentiate CTEPH from PAH (AUC = 0.849, sensitivity = 78%, specificity = 88%).**

Conclusion: **Postural changes in ventilatory gas analysis are useful as a non-invasive bedside evaluation to screen for the presence of PH and distinguish between CTEPH and PAH.**

SUMMARY AT A GLANCE

Differentiating between chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH) using non-invasive techniques remains challenging. Ventilatory gas analysis in different postures is a useful, non-invasive bedside method to screen for the presence of pulmonary hypertension (PH) and distinguish between CTEPH and PAH.

Key words: cardiovascular diseases, pulmonary circulation, pulmonary hypertension, pulmonary ventilation, pulmonary gas exchange.

INTRODUCTION

Pulmonary hypertension (PH) has a poor prognosis due to increased pulmonary arterial pressure (PAP), which causes progressive right heart failure.[1–3] Chronic thromboembolic PH (CTEPH) and pulmonary arterial hypertension (PAH) are two subtypes of PH. CTEPH is characterized by organic thrombotic obstructions of pulmonary arteries, which reduce pulmonary vascular reserve.[4] Recently, balloon pulmonary angioplasty has been reported to improve long-term prognosis and respiratory function in patients with inoperable CTEPH; thus, CTEPH treatment has entered a new era.[5,6] CTEPH is the only potentially curable type of PH.[7] As new therapies are developed for CTEPH and PAH, screening for the presence of PH, prompt diagnosis and distinction between CTEPH and PAH have become increasingly important. Although their pathophysiology differs, the clinical presentation of CTEPH is similar to that of PAH; both disorders have non-specific symptoms. The diagnosis of CTEPH is based on the presence of PH established by right heart catheterization (RHC), mismatched perfusion defects on ventilation/perfusion (V/Q) scan and specific diagnostic signs of CTEPH on multidetector computed tomography (CT) angiography,

Correspondence: Masahiro Kohzuki, Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. Email: kohzuki@med.tohoku.ac.jp

Received 7 November 2018; invited to revise 22 January, 18 March and 18 April 2019; revised 26 February, 25 March and 25 April 2019; accepted 22 May 2019 (Associate Editor: Helen Whitford; Senior Editor: Yuben Moodley)

magnetic resonance imaging or conventional pulmonary cineangiography.[3] However, these examinations are invasive or associated with substantial patient burden. Therefore, the non-invasive differentiation between CTEPH and PAH still remains challenging.

Generally, postural change from sitting to supine improves the V/Q mismatch because of pulmonary perfusion redistribution, reflecting functional pulmonary vascular reserves.[8] Meanwhile, decreased pulmonary vascular reserve leads to the attenuation of the redistribution of pulmonary perfusion through postural change.[4] The degree of perfusion redistribution with postural change is correlated with PH severity.[9] Moreover, non-invasive measurement of end-tidal CO_2 pressure ($P_{ET}CO_2$) reflects pulmonary blood flow and V/Q mismatch.[10,11] Cardiopulmonary exercise testing with ventilatory gas analysis could not only detect CTEPH despite normal echocardiography, but also discriminate PAH and CTEPH from differences in ventilation efficiency.[12–15] Therefore, combining measures of postural changes in ventilatory gas analysis parameters could be another useful non-invasive method to screen for the presence of PH and differentiate PAH from CTEPH.

Thus, we examined whether postural changes in ventilatory gas analysis are useful in developing a non-invasive bedside screening method for the presence of PH and distinguishing between PAH and CTEPH.

METHODS

Study subjects

Patients with suspected PH were prospectively enrolled from September 2015 to June 2018. In total, 25 patients with newly diagnosed PAH, 40 patients with newly diagnosed CTEPH and 25 non-PH patients were included. Diagnoses were based on published clinical guidelines.[3] Non-PH patients are those with suspected PH but with normal mean PAP (mPAP) values (i.e. <25 mm Hg). Patients with other PH forms, respiratory disease, a constant need for supplemental oxygen or oxygen saturation (SpO_2) <85% in ambient air were excluded. We performed RHC, echocardiography and ventilatory gas analysis, with patients in the sitting and supine positions, within 3 days before or after RHC.

This study was performed according to the principles of the Declaration of Helsinki. The study protocol (No. 2016-1-254) was approved by the ethics committee of Tohoku University Graduate School of Medicine. All patients provided written informed consent.

Right heart catheterization

RHC was performed with a 6-Fr Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) in the supine position. We measured the mPAP, pulmonary vascular resistance and cardiac output with the indirect Fick method, which was corrected for body surface area (cardiac index). Upon diagnosis, no patients had intracardiac shunt.

We measured arterial oxygen (O_2) partial pressure (PaO_2) in the artery and pulmonary artery; blood gas analyses were performed using arterial and pulmonary arterial blood samples obtained during RHC in room air. To calculate intrapulmonary shunt, O_2 was given with a reservoir mask at 10 L/min for 5 min.[16] To minimize the influence of variation in arterial O_2 saturation (SaO_2) on the intrapulmonary shunt, we used intrapulmonary shunt during O_2 administration. Thereafter, we performed blood gas analyses again to obtain intrapulmonary shunt, which was calculated as follows[16]:

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

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

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

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

where Hb represents haemoglobin (g/dL), SvO_2 mixed venous O_2 saturation, P_AO_2 alveolar O_2 partial pressure and PvO_2 represents the mixed venous O_2 partial pressure.

Ventilatory gas analysis and echocardiography

Ventilatory gas analysis was performed with an expired gas analyser (AE-100i, Minato Ikagaku, Osaka, Japan) in the sitting and supine positions. Ventilatory gas parameters, including minute ventilation, tidal volume, respiratory rate, oxygen uptake, carbon dioxide output and $P_{ET}CO_2$, were measured continuously with a breath-by-breath method. From these data, derived variables, including ratio of ventilation to CO_2 production (VE/VCO_2), were calculated. SpO_2 was measured continuously using pulse oximetry.

Patients wear the mask, and ventilatory gas analysis data on 5-min sitting position followed by 5-min supine position were continuously recorded. Patients were instructed to maintain normal tidal breathing during the analysis. After 5-min recording for each position, ventilatory gas analysis values of the mean of the recording at the last 1 min at each position were calculated. Differences in ventilatory gas analysis parameters between the sitting and supine positions were defined as follows: (Δ(supine − sitting)).

Subjects underwent a standard echocardiographic examination according to the American Society of Echocardiography and European Association of Echocardiography recommendations.[17,18] Echocardiographic parameters, including ejection fractions, right ventricular fractional area change (RVFAC), tricuspid valve regurgitation pressure gradient (TRPG) and tricuspid annular plane systolic excursion, were measured.

Statistical analysis

Results are expressed as means ± SD. Statistical analysis was performed using SPSS ver. 21 (IBM Corp., Armonk, NY, USA). Differences among groups were compared using one-way analysis of variance followed by a Bonferroni test. Postural changes in ventilatory gas parameters were examined using a repeated-measures analysis of variance with postural change as a within-

subject effect and group as a between-subject effect. Bonferroni test was employed for post hoc analysis when significant differences were found. The association between haemodynamics and ventilatory gas parameters was determined using Spearman's correlations. To assess the utility of ventilatory gas analysis for PH and CTEPH prediction, receiver operating characteristic (ROC) curves were generated. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

We prospectively enrolled 90 patients with suspected PH. Diagnoses included PAH ($n = 25$), CTEPH ($n = 40$) and non-PH ($n = 25$). Baseline characteristics and haemodynamic parameters are shown in Table 1. The 25 PAH cases included idiopathic PAH ($n = 14$) and PAH associated with connective tissue disease ($n = 9$), congenital heart disease ($n = 1$) and porto-PH ($n = 1$). The non-PH group consisted of patients with dyspnoea and abnormal echocardiographic parameters. Some patients had connective tissue disease ($n = 13/25$) and pulmonary embolism ($n = 2/25$).

PAH patients were younger than CTEPH patients ($P < 0.001$). No significant differences in the haemodynamic and echocardiographic parameters between the PAH and CTEPH groups were found. Intrapulmonary shunt in CTEPH was significantly higher than that in PAH ($P < 0.001$). The PAH group had lower % diffusing capacity of the lung for carbon monoxide (DL_{CO}) than the non-PH and CTEPH groups ($P = 0.010$ and $P < 0.001$, respectively).

Ventilatory gas parameters in sitting and supine positions

Sitting and supine $P_{ET}CO_2$ differed significantly among the groups (all $P < 0.001$). $P_{ET}CO_2$ significantly

Table 1 Baseline characteristics of enrolled patients

Characteristics	Non-PH ($n = 25$)	PAH ($n = 25$)	CTEPH ($n = 40$)
Female : male (*n*)	23:2	22:3	36:4
Age (years)	62.3 ± 16.0	49.7 ± 20.4*	66.6 ± 12.8****
mPAP (mm Hg)	18.0 ± 3.5	44.0 ± 14.0**	38.6 ± 9.3**
PVR (dyne/s/cm^5)	155 ± 56	753 ± 374**	715 ± 310**
CO (mL/min)	4.05 ± 1.09	3.42 ± 1.21	3.27 ± 1.00*
CI (L/min/m^2)	2.76 ± 0.68	2.31 ± 0.73*	2.16 ± 0.54**
SvO_2 (%)	71.7 ± 5.1	64.1 ± 8.3**	61.4 ± 7.3**
PvO_2 (mm Hg)	40.6 ± 3.4	36.5 ± 4.9**	34.3 ± 3.5**
SaO_2 (%)	95.9 ± 2.4	92.6 ± 3.5**	88.8 ± 4.5**,****
PaO_2 (mm Hg)	86.0 ± 11.6	67.9 ± 9.5**	57.1 ± 10.2**,****
$PaCO_2$ (mm Hg)	39.6 ± 3.0	35.8 ± 4.0**	36.0 ± 5.1**
Intrapulmonary shunt (%)	13.8 ± 5.5	21.6 ± 6.6**	30.0 ± 9.2**,****
EF (%)	64.2 ± 12.6	70.7 ± 9.1	69.8 ± 8.0
RVFAC (%)	42.2 ± 8.3	25.4 ± 10.0**	27.6 ± 9.1**
TAPSE (mm)	21.3 ± 4.5	18.3 ± 5.1	18.0 ± 4.1*
TRPG (mm Hg)	33.6 ± 11.2	69.4 ± 26.1**	69.4 ± 28.2**
$\%DL_{CO}$	83.2 ± 24.5	62.1 ± 19.0*	92.4 ± 23.3****
6MWD (m)	521 ± 97	398 ± 126**	366 ± 126**
Sitting VE (L/min)	8.7 ± 1.8	9.8 ± 2.6	10.2 ± 1.9**
Supine VE (L/min)	8.3 ± 2.0	9.4 ± 1.9	10.3 ± 1.7**
Sitting RR (f/min)	17.9 ± 4.7	18.8 ± 5.6	16.0 ± 4.4
Supine RR (f/min)	15.1 ± 4.1	17.7 ± 4.5	16.9 ± 5.0
Sitting $P_{ET}CO_2$ (mm Hg)	35.2 ± 3.1	31.5 ± 3.4**	29.5 ± 2.9**,***
Supine $P_{ET}CO_2$ (mm Hg)	37.5 ± 3.4	31.2 ± 3.6**	28.0 ± 3.0**,****
Sitting VE/VCO_2	49.2 ± 9.3	54.6 ± 10.0	53.8 ± 8.1
Supine VE/VCO_2	43.2 ± 8.3	51.8 ± 9.0**	57.3 ± 9.7**
Sitting SpO_2 (%)	96.3 ± 2.0	94.1 ± 2.7**	94.2 ± 2.6**
Supine SpO_2 (%)	96.4 ± 2.3	94.4 ± 2.4	92.5 ± 3.5**,****

*$P < 0.05$ versus non-PH; **$P < 0.01$ versus non-PH; ***$P < 0.05$ versus PAH; ****$P < 0.01$ versus PAH.

Values are expressed as mean ± SD.

6MWD, 6-min walk distance; CI, cardiac index; CO, cardiac output; CTEPH, chronic thromboembolic PH; DL_{CO}, diffusing capacity of the lung for carbon monoxide; EF, ejection fraction; mPAP, mean pulmonary arterial pressure; $PaCO_2$, arterial CO_2 partial pressure; PAH, pulmonary arterial hypertension; PaO_2, arterial O_2 partial pressure; $P_{ET}CO_2$, end-tidal CO_2 pressure; PH, pulmonary hypertension; 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; SpO_2, oxygen saturation; SvO_2, mixed venous O_2 saturation; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid valve regurgitation pressure gradient; VE, minute ventilation; VE/VCO_2, ratio of ventilation to CO_2 production.

decreased with postural change in the CTEPH group ($P < 0.001$), whereas no significant difference with postural change in the PAH group was observed ($P = 0.193$). Moreover, $P_{ET}CO_2$ significantly increased with postural change in the non-PH group ($P < 0.001$). $\Delta P_{ET}CO_2$ significantly differed among the three groups (all $P < 0.001$) (Fig. 1A).

CTEPH and PAH groups presented higher supine VE/VCO_2 than the non-PH group ($P < 0.001$ and $P = 0.004$, respectively). VE/VCO_2 significantly increased with postural change in the CTEPH group ($P < 0.001$). By contrast, VE/VCO_2 significantly decreased in the non-PH and PAH groups (both $P < 0.001$). $\Delta VE/VCO_2$ was comparable between the non-PH and PAH groups. However, $\Delta VE/VCO_2$ in CTEPH was significantly different from that in the other two groups (Fig. 1B).

The CTEPH group had lower supine SpO_2 than the non-PH and PAH groups ($P < 0.001$ and $P = 0.029$, respectively). Moreover, SpO_2 significantly decreased with postural change in the CTEPH group ($P < 0.001$), whereas no significant difference was found during postural change in the non-PH and PAH groups ($P = 0.543$ and $P = 0.488$, respectively).

Intrapulmonary shunt was correlated with mPAP ($R^2 = 0.197$, $P < 0.001$) (Fig. 2). A significant negative correlation between intrapulmonary shunt and sitting $P_{ET}CO_2$ ($R^2 = 0.197$, $P < 0.001$) and supine $P_{ET}CO_2$ ($R^2 = 0.282$, $P < 0.001$), and between intrapulmonary shunt and $\Delta P_{ET}CO_2$ ($R^2 = 0.166$, $P < 0.001$) was found (Fig. 3A,B). Moreover, significant positive correlation between intrapulmonary shunt and supine VE/VCO_2 ($R^2 = 0.134$, $P < 0.001$) and $\Delta VE/VCO_2$ ($R^2 = 0.166$, $P < 0.001$) was noted (Fig. 3C,D). A significant negative correlation between intrapulmonary shunt and sitting SpO_2 ($R^2 = 0.100$, $P = 0.003$) and supine SpO_2 ($R^2 = 0.197$, $P < 0.001$), and between intrapulmonary shunt and ΔSpO_2 ($R^2 = 0.132$, $P < 0.001$) was found.

Ventilatory gas analysis parameters for discriminating PH from non-PH

An ROC curve was generated to evaluate the ability of ventilatory gas parameters to distinguish between the non-PH and PH groups (i.e. PAH and CTEPH). Using $\Delta P_{ET}CO_2$, the area under the curve (AUC) was 0.969 with 89% sensitivity and 100% specificity at an optimal cut-off point of 0 mm Hg ($P < 0.001$) (Fig. 4A). Data for the area under the ROC curve for echocardiographic parameters to distinguish between the non-PH and PH groups were as follows: $AUC_{TRPG} = 0.894$, $P < 0.001$ and $AUC_{RVFAC} = 0.925$, $P < 0.001$. $\Delta P_{ET}CO_2$ was the best predictor of PH.

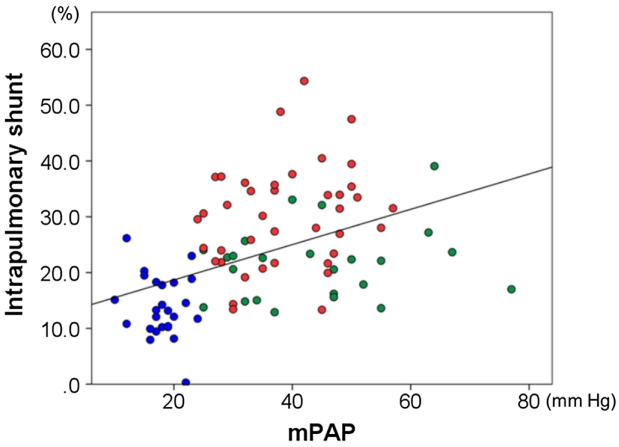

Figure 2 Correlation between mPAP and intrapulmonary shunt ($R^2 = 0.197$, $P < 0.001$). ●, Non-PH; ●, PAH; ●, CTEPH. CTEPH, chronic thromboembolic PH; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

Differences in ventilatory gas analysis between PAH and CTEPH

Sitting and supine $P_{ET}CO_2$ in CTEPH were significantly lower than those in PAH ($P = 0.031$ and $P = 0.001$, respectively) (Table 1). Moreover, CTEPH presented with lower $\Delta P_{ET}CO_2$ and higher $\Delta VE/VCO_2$ than PAH, although no differences in haemodynamic and echocardiographic parameters between the two groups were noted ($P = 0.001$ and $P < 0.001$, respectively) (Table 1, Fig. 1). $\Delta VE/VCO_2 > 0.8$ could effectively differentiate CTEPH from PAH (AUC = 0.849, sensitivity = 78% and specificity = 88%) (Fig. 4B).

DISCUSSION

The novel findings of this study are as follows: (i) $\Delta P_{ET}CO_2$ is useful to distinguish between PH and

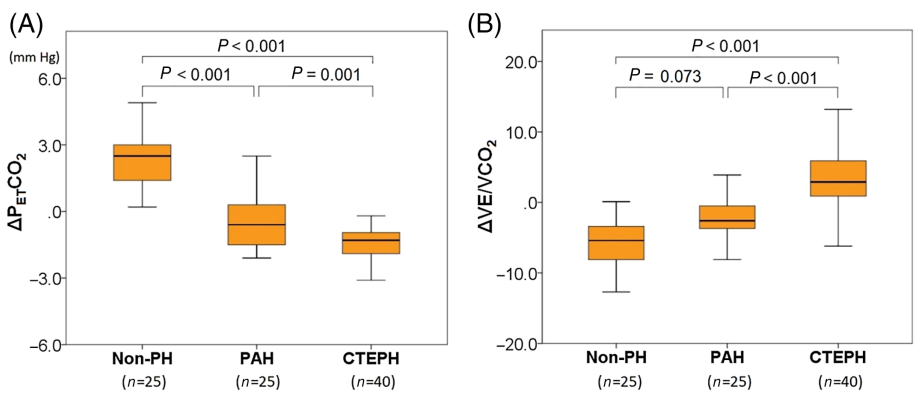

Figure 1 Comparison of supine $\Delta P_{ET}CO_2$ (A) and $\Delta VE/VCO_2$ (B) by patient subgroups. CTEPH, chronic thromboembolic PH; PAH, pulmonary arterial hypertension; $P_{ET}CO_2$, end-tidal CO_2 pressure; PH, pulmonary hypertension; VE/VCO_2, ratio of ventilation to CO_2 production.

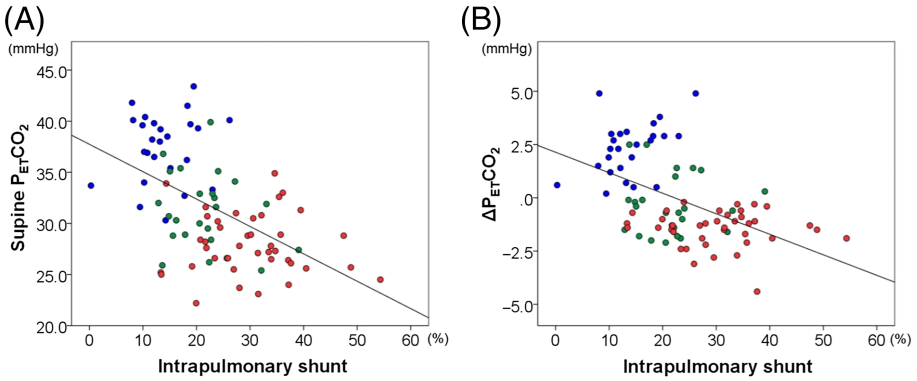

Figure 3 Correlation between intrapulmonary shunt and supine $P_{ET}CO_2$ (R^2 = 0.282, P < 0.001) (A), intrapulmonary shunt and $\Delta P_{ET}CO_2$ (R^2 = 0.257, P < 0.001) (B), intrapulmonary shunt and supine VE/VCO_2 (R^2 = 0.134, P < 0.001) (C) and intrapulmonary shunt and $\Delta VE/VCO_2$ (R^2 = 0.166, P < 0.001) (D). ●, Non-PH; ●, PAH; ●, CTEPH. CTEPH, chronic thromboembolic PH; PAH, pulmonary arterial hypertension; $P_{ET}CO_2$, end-tidal CO_2 pressure; PH, pulmonary hypertension; VE/VCO_2, ratio of ventilation to CO_2 production.

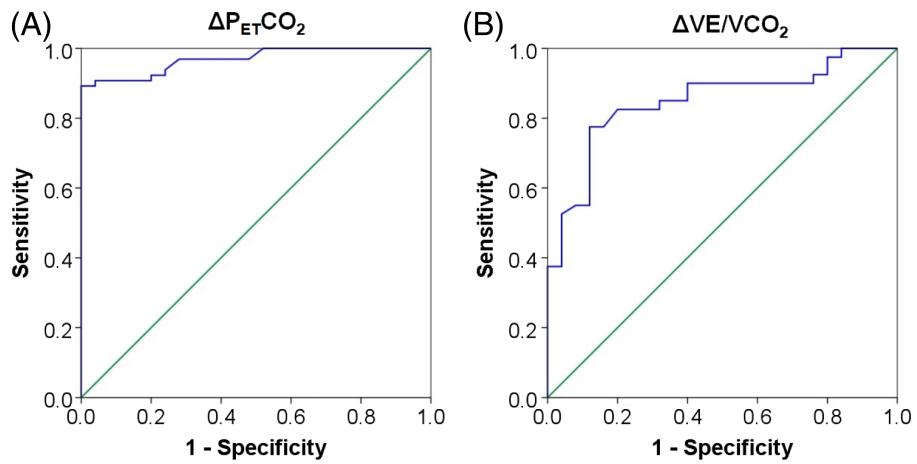

Figure 4 ROC curves of $\Delta P_{ET}CO_2$ for discriminating non-PH versus PH groups (AUC = 0.969, P < 0.001) (A) and $\Delta VE/VCO_2$ for discriminating PAH versus CTEPH groups (AUC = 0.849, P < 0.001) (B). AUC, area under the curve; CTEPH, chronic thromboembolic PH; PAH, pulmonary arterial hypertension; $P_{ET}CO_2$, end-tidal CO_2 pressure; PH, pulmonary hypertension; ROC, receiver operating characteristic; VE/VCO_2, ratio of ventilation to CO_2 production.

non-PH and (ii) $\Delta VE/VCO_2$ could effectively differentiate CTEPH from PAH. To our knowledge, this is the first study to demonstrate that ventilatory gas analysis in different postures is a useful non-invasive bedside evaluation to screen for the presence of PH and distinguish CTEPH from PAH.

Distinguishing between PH and non-PH

Increased resting PAP is a late marker of pulmonary vascular disease because approximately half of the pulmonary circulation must be obstructed before an increase in resting PAP is detected.[19–22] However, several screening modalities are dependent on increased PAP and thus fail with mild PAP increase at an early stage of PH.[23,24] Cardiopulmonary exercise testing using ventilator gas analysis is a useful diagnostic tool for CTEPH detection in patients with suspected PH without abnormal echocardiography findings.[14] However, in exercise tests, clinicians may sometimes add more load than expected in critically ill PH patients. A previous study showed that quantifying the degree of perfusion redistribution through postural change with single-photon emission CT/CT may be useful for the assessment of functional pulmonary vascular reserve, and the results may correlate well with disease severity.[9] Compared with the evaluation of parameters in only one posture, the posture change method is superior in discriminating between normal values and PH.[9]

Postural change from sitting to supine position usually improves V/Q mismatch because of pulmonary vascular reserve and increased functional pulmonary blood flow (Fig. 5).[25–27] These changes result in increased $P_{ET}CO_2$ and decreased VE/VCO_2. In this study, $P_{ET}CO_2$ significantly increased and VE/VCO_2 significantly decreased with postural change in the non-

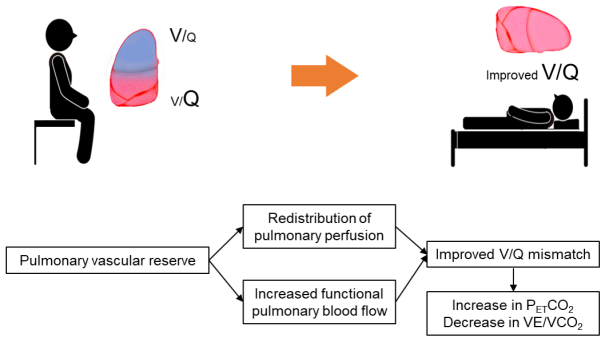

Figure 5 Schematic diagram of the changes in V/Q mismatch and ventilatory gas parameters by postural changes. $P_{ET}CO_2$, end-tidal CO_2 pressure, VE/VCO_2, ratio of ventilation to CO_2 production, V/Q, ventilation/perfusion.

PH group. Moreover, $\Delta P_{ET}CO_2$ was significantly lower in the CTEPH and PAH groups than in the non-PH group (both $P < 0.0001$) (Fig. 2). Furthermore, $\Delta P_{ET}CO_2 < 0$ mm Hg could effectively differentiate PH from non-PH (Fig. 4A). This finding shows that a low $\Delta P_{ET}CO_2$ may be a useful non-invasive marker to evaluate the presence of PH.

Differentiating CTEPH from PAH

Several studies showed significant differences in exercise gas exchanges between PAH and CTEPH.[12,15,28] Scheidl *et al.* reported that capillary to end-tidal carbon dioxide gradients indicating heterogeneous pulmonary perfusion may help distinguish CTEPH from PAH based on resting and exercise values.[29]

In this study, different changes in ventilatory gas parameters by postural change between CTEPH and PAH patients could be explained by the more pronounced intrapulmonary shunt in CTEPH. CTEPH is known to have intrapulmonary shunts where shunt flow via pre-existing arteriovenous anastomosis is increased by elevated PAP.[30–32] Moreover, the total area of the bronchial artery is significantly greater in CTEPH than in PAH.[33,34] In our study, intrapulmonary shunt increased as mPAP increased, greater in CTEPH than in PAH, and correlated with mPAP (Table 1, Fig. 2).

Intrapulmonary shunt could result in lower $P_{ET}CO_2$ and higher VE/VCO_2 values.[35] Moreover, the effects of intrapulmonary shunts on pulmonary circulation and gas exchange are made apparent by posture change.[36] In this study, postural change from sitting to supine significantly decreased $P_{ET}CO_2$ and increased VE/VCO_2 in the CTEPH group. However, $P_{ET}CO_2$ remained unchanged and VE/VCO_2 significantly decreased in the PAH group. Moreover, various ventilatory gas parameters were correlated with intrapulmonary shunt (Fig. 3). Notably, these parameters were significantly different between the PAH and CTEPH groups, whereas the haemodynamic and echocardiographic parameters were comparable between these groups (Table 1, Fig. 1). Furthermore, $\Delta VE/VCO_2$ could effectively differentiate CTEPH from PAH (Fig. 4B). A posture-induced increase in intrapulmonary shunt that occurs during supine helps decrease $P_{ET}CO_2$ and increase VE/VCO_2, and leads to a difference in the ventilatory gas analysis parameters with postural change by intrapulmonary shunt amount. Moreover, these changes were more prominent in CTEPH, which has greater intrapulmonary shunt than in PAH.

Utility of the ventilatory gas analysis with postural change

In summary, patients with $\Delta P_{ET}CO_2 < 0$ mm Hg would likely have PH and those with $\Delta VE/VCO_2 > 0.8$ are classified as patients with suspected CTEPH. The present postural change method is easy to perform at bedside, safe and feasible in clinical practice. Thus, this method may be a useful non-invasive bedside strategy to screen for the presence of PH and distinguish CTEPH from PAH.

Study limitations

This study has several limitations. First, this is a single-centre study with a relatively small sample size. Thus, the non-PH group included patients who had a history of pulmonary embolism and were not fully characterized. Moreover, patients with chronic thromboembolic disease with persistent pulmonary thromboembolic occlusions with near-normal pulmonary haemodynamics at rest experience breathlessness and low $P_{ET}CO_2$ during exercise.[37,38] However, showing the differences between PH and non-PH with suspected PH is of even greater value. With this, the findings need to be confirmed in future multicentre studies with a large sample. Second, we failed to evaluate patients with severe hypoxaemia requiring persistent oxygen supplementation at rest. Third, we did not directly measure intrapulmonary shunt change in sitting and supine positions using blood gas analysis. Fourth, the CTEPH group is naturally significantly older than the PAH group. As reported, VE/VCO_2 is affected by age.[39] Thus, age difference might have affected our results. Finally, we did not examine the presence of patent foramen ovale (PFO) that occasionally induces hypoxaemia by postural change. The reported PFO prevalence among PAH patients is 27%.[40] Although not all PFO patients show hypoxaemia by postural change, those with PFO might affect the results of the present study.

In conclusion, ventilatory gas analysis in different postures is a useful non-invasive method to screen for the presence of PH and distinguish CTEPH from PAH. This novel method may have important clinical applications, such as being an initial step in the diagnosis of CTEPH.

Acknowledgement: This work was supported by JSPS KAKENHI (Grant Number 17K13047).

Author contributions: Conceptualization: M.A., K.S., T.A. Formal analysis: M.A., T.A. Funding acquisition: M.A. Investigation: M.A., S.T., S.Y., H.S. Methodology: M.A., K.S., T.A. Supervision: M.K., H.S., K.S. Visualization: M.A., T.K. Writing—original draft: M.A., K.S. Writing—review and editing: M.A., K.S., H.S., M.K.

Abbreviations: AUC, area under the curve; CaO_2, arterial O_2 content; CcO_2, pulmonary capillary O_2 content; CT, computed tomography; CTEPH, chronic thromboembolic PH; mPAP, mean

PAP; PAH, pulmonary arterial hypertension; PaO_2, arterial O_2 partial pressure; P_AO_2, alveolar O_2 partial pressure; PAP, pulmonary arterial pressure; $P_{ET}CO_2$, end-tidal CO_2 pressure; PFO, patent foramen ovale; PH, pulmonary hypertension; RHC, right heart catheterization; ROC, receiver operating characteristic; RR, respiratory rate; RVFAC, right ventricular fractional area change; SaO_2, arterial O_2 saturation; SpO_2, oxygen saturation; TRPG, tricuspid valve regurgitation pressure gradient; V/Q, ventilation/perfusion; VE, minute ventilation; VE/VCO_2, ratio of ventilation to CO_2 production.

REFERENCES

1 Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Circulation* 2006; **113**: 2011–20.
2 Jenkins D, Mayer E, Screaton N, Madani M. State-of-the-art chronic thromboembolic pulmonary hypertension diagnosis and management. *Eur. Respir. Rev.* 2012; **21**: 32–9.
3 Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M *et al.*; ESC Scientific Document Group. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur. Heart J.* 2016; **37:** 67–119.
4 Simonneau G, Torbicki A, Dorfmuller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur. Respir. Rev.* 2017; **26**: pii: 160112.
5 Aoki T, Sugimura K, Tatebe S, Miura M, Yamamoto S, Yaoita N, Suzuki H, Sato H, Kozu K, Konno R *et al.* Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension: long-term effects and procedure-related complications. *Eur. Heart J.* 2017; **38**: 3152–9.
6 Akizuki M, Serizawa N, Ueno A, Adachi T, Hagiwara N. Effect of balloon pulmonary angioplasty on respiratory function in patients with chronic thromboembolic pulmonary hypertension. *Chest* 2017; **151**: 643–9.
7 Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V *et al.* Chronic thromboembolic pulmonary hypertension. *J. Am. Coll. Cardiol.* 2013; **62**: D92–9.
8 Petersson J, Rohdin M, Sanchez-Crespo A, Nyren S, Jacobsson H, Larsson SA, Lindahl SG, Linnarsson D, Neradilek B, Polissar NL *et al.* Regional lung blood flow and ventilation in upright humans studied with quantitative SPECT. *Respir. Physiol. Neurobiol.* 2009; **166**: 54–60.
9 Lau EM, Bailey DL, Bailey EA, Torzillo PJ, Roach PJ, Schembri GP, Corte TJ, Celermajer DS. Pulmonary hypertension leads to a loss of gravity dependent redistribution of regional lung perfusion: a SPECT/CT study. *Heart* 2014; **100**: 47–53.
10 Matsumoto A, Itoh H, Eto Y, Kobayashi T, Kato M, Omata M, Watanabe H, Kato K, S M. End-tidal CO2 pressure decreases during exercise in cardiac patients. *J. Am. Coll. Cardiol.* 2000; **36**: 242–9.
11 Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest* 2005; **127**: 1637–46.
12 Zhai Z, Murphy K, Tighe H, Wang C, Wilkins MR, Gibbs JSR, Howard LS. Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 2011; **140**: 1284–91.
13 Zhao QH, Wang L, Pudasaini B, Jiang R, Yuan P, Gong SG, Guo J, Xiao Q, Liu H, Wu C *et al.* Cardiopulmonary exercise testing improves diagnostic specificity in patients with echocardiography-suspected pulmonary hypertension. *Clin. Cardiol.* 2017; **40**: 95–101.
14 Held M, Grun M, Holl R, Hubner G, Kaiser R, Karl S, Kolb M, Schafers HJ, Wilkens H, Jany B. Cardiopulmonary exercise testing to detect chronic thromboembolic pulmonary hypertension in patients with normal echocardiography. *Respiration* 2014; **87**: 379–87.
15 Shi X, Guo J, Gong S, Sapkota R, Yang W, Liu H, Xiang W, Wang L, Sun X, Liu J. Oxygen uptake is more efficient in idiopathic pulmonary arterial hypertension than in chronic thromboembolic pulmonary hypertension. *Respirology* 2016; **21**: 149–56.
16 Vodoz JF, Cottin V, Glerant JC, Derumeaux G, Khouatra C, Blanchet AS, Mastroianni B, Bayle JY, Mornex JF, Cordier JF. Right-to-left shunt with hypoxemia in pulmonary hypertension. *BMC Cardiovasc. Disord.* 2009; **9**: 15.
17 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS *et al.*; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J. Am. Soc. Echocardiogr.* 2005; **18:** 1440–63.
18 Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J. Am. Soc. Echocardiogr.* 2010; **23**: 685–713; quiz 786–8.
19 Burrowes KS, Clark AR, Marcinkowski A, Wilsher ML, Milne DG, Tawhai MH. Pulmonary embolism: predicting disease severity. *Philos. Trans. A Math. Phys. Eng. Sci.* 2011; **369**: 4255–77.
20 MDM D, Verhaege R, Verleden GM. *Pulmonary Vascular Pathology: A Clinical Update*. UK, European Respiratory Society Journals Ltd, 2004.
21 Frazier AA, Galvin JR, Franks TJ, Rosado-De-Christenson ML. From the archives of the AFIP: pulmonary vasculature: hypertension and infarction. *Radiographics* 2000; **20**: 491–524; quiz 530–1, 532.
22 Lau EM, Manes A, Celermajer DS, Galie N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. *Eur. Heart J.* 2011; **32**: 2489–98.
23 Grünig E, Barner A, Bell M, Claussen M, Dandel M, Dumitrescu D, Gorenflo M, Holt S, Kovacs G, Ley S *et al.* Non-invasive diagnosis of pulmonary hypertension: ESC/ERS guidelines with Updated Commentary of the Cologne Consensus Conference 2011. *Int. J. Cardiol.* 2011; **154**: S3–12.
24 Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. *Eur. Respir. Rev.* 2017; **26**: pii: 160108.
25 Gisolf J, Wilders R, Immink RV, van Lieshout JJ, Karemaker JM. Tidal volume, cardiac output and functional residual capacity determine end-tidal CO2 transient during standing up in humans. *J. Physiol.* 2004; **554**: 579–90.
26 Immink RV, Secher NH, Roos CM, Pott F, Madsen PL, van Lieshout JJ. The postural reduction in middle cerebral artery blood velocity is not explained by PaCO2. *Eur. J. Appl. Physiol.* 2006; **96**: 609–14.
27 Immink RV, Truijen J, Secher NH, Van Lieshout JJ. Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion. *J. Appl. Physiol. (1985)* 2009; **107**: 816–23.
28 Godinas L, Sattler C, Lau EM, Jaïs X, Taniguchi Y, Jevnikar M, Weatherald J, Sitbon O, Savale L, Montani D *et al.* Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension. *J. Heart Lung Transplant.* 2017; **36**: 1234–42.
29 Scheidl SJ, Englisch C, Kovacs G, Reichenberger F, Schulz R, Breithecker A, Ghofrani H-A, Seeger W, Olschewski H. Diagnosis

of CTEPH versus IPAH using capillary to end-tidal carbon dioxide gradients. *Eur. Respir. J.* 2012; **39**: 119–24.
30 Aoki T, Sugimura K, Nochioka K, Miura M, Tatebe S, Yamamoto S, Yaoita N, Suzuki H, Sato H, Kozu K *et al*. Effects of balloon pulmonary angioplasty on oxygenation in patients with chronic thromboembolic pulmonary hypertension – importance of intrapulmonary shunt. *Circ. J.* 2016; **80**: 2227–34.
31 Elliott CG. Pulmonary physiology during pulmonary embolism. *Chest* 1992; **101**: 163S–71S.
32 Dorfmüller P, Günther S, Ghigna M-R, Thomas de Montpréville V, Boulate D, Paul J-F, Jaïs X, Decante B, Simonneau G, Dartevelle P *et al*. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. *Eur. Respir. J.* 2014; **44**: 1275–88.
33 Shimizu H, Tanabe N, Terada J, Masuda M, Sakao S, Kasahara Y, Takiguchi Y, Tatsumi K, Kuriyama T. Dilatation of bronchial arteries correlates with extent of central disease in patients with chronic thromboembolic pulmonary hypertension. *Circ. J.* 2008; **72**: 1136–41.
34 Grosse A, Grosse C, Lang IM. Distinguishing chronic thromboembolic pulmonary hypertension from other causes of pulmonary hypertension using CT. *AJR Am. J. Roentgenol.* 2017; **209**: 1228–38.
35 Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation* 2002; **105**: 54–60.
36 Lovering AT, Duke JW, Elliott JE. Intrapulmonary arteriovenous anastomoses in humans – response to exercise and the environment. *J. Physiol.* 2015; **593**: 507–20.
37 McCabe C, Deboeck G, Harvey I, Ross RM, Gopalan D, Screaton N, Pepke-Zaba J. Inefficient exercise gas exchange identifies pulmonary hypertension in chronic thromboembolic obstruction following pulmonary embolism. *Thromb. Res.* 2013; **132**: 659–65.
38 Taboada D, Pepke-Zaba J, Jenkins DP, Berman M, Treacy CM, Cannon JE, Toshner M, Dunning JJ, Ng C, Tsui SS *et al*. Outcome of pulmonary endarterectomy in symptomatic chronic thromboembolic disease. *Eur. Respir. J.* 2014; **44**: 1635–45.
39 Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *Am. J. Respir. Crit. Care Med.* 2002; **166**: 1443–8.
40 Gallo de Moraes A, Vakil A, Moua T. Patent foramen ovale in idiopathic pulmonary arterial hypertension: long-term risk and morbidity. *Respir. Med.* 2016; **118**: 53–7.

Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Visual Abstract Non-invasive screening using ventilatory gas analysis to distinguish between CTEPH and PAH.

