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Diagnosis of CTEPH *versus* IPAH using capillary to end-tidal carbon dioxide gradients

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ABSTRACT: Chronic thromboembolic pulmonary hypertension (CTEPH) represents an important differential diagnosis to idiopathic pulmonary arterial hypertension (IPAH). We hypothesised that the capillary to end-tidal carbon dioxide gradient at rest and during exercise might help differentiate CTEPH from IPAH.

Patients who presented with unequivocal IPAH or CTEPH according to ventilation/perfusion scanning, pulmonary angiography, computed tomography and right heart catheterisation were included in this retrospective study and compared with healthy controls.

21 IPAH patients and 16 CTEPH patients fulfilled the inclusion criteria. Haemodynamics and peak oxygen uptake were comparable, but respiratory rates at rest and during exercise were significantly higher in CTEPH than in IPAH. End-tidal carbon dioxide was significantly lower in CTEPH *versus* IPAH at rest and during exercise, while capillary carbon dioxide values were similar. Correspondingly, capillary to end-tidal carbon dioxide gradients were significantly increased in CTEPH *versus* IPAH at rest and during exercise (median (range) 8.6 (3.0–13.7) *versus* 4.4 (0.9–9.0) ($p<0.001$) and 9.3 (3.3–13.1) *versus* 4.1 (0.0–8.8) mmHg ($p<0.001$), respectively). Although these values were closer to normal in IPAH they were still significantly elevated compared with healthy controls (2.3 (-4.8–8.1) and -1.9 (-5.7–6.2) mmHg, respectively).

Capillary to end-tidal carbon dioxide gradients may help to distinguish CTEPH from IPAH based on resting and exercise values.

KEYWORDS: Blood gas analysis, exercise test, pulmonary hypertension

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Pulmonary hypertension is a devastating disease that may be caused by thromboembolic events leading to chronic thromboembolic pulmonary hypertension (CTEPH). Among patients referred to a pulmonary hypertension clinic, the majority suffer from two distinct diseases, CTEPH and idiopathic pulmonary arterial hypertension (IPAH) [1]. In our experience, scleroderma, congenital heart disease, portal hypertension, HIV, appetite suppressants and other associated factors represent a smaller proportion. Although the aetiology of CTEPH clearly differs from other forms of pulmonary hypertension, the diagnosis of CTEPH may be challenging. When we consider the rate of CTEPH after symptomatic acute lung embolism, which may amount to 3.6% [2], and that only 50–80% of CTEPH patients are aware of a thromboembolic event [3–5], we may assume that this disease is dramatically underdiagnosed. This aspect gains even more importance as CTEPH can be prevented by anticoagulation and treated by pulmonary endarterectomy [5, 6], a highly effective but demanding operation that requires special diagnostic measures. Application of methods detecting perfusion heterogeneity might contribute to early identification of these patients and timely initiation of an optimised diagnostic and therapeutic strategy.

In CTEPH, there is heterogeneous blood flow in the lungs. Areas with diminished blood flow and areas with increased blood flow coexist, while ventilation is more or less homogeneously distributed. As a result, there are areas with an increased ventilation/perfusion ratio or even dead space ventilation and others with a low ventilation/perfusion ratio. Dead space ventilation increases the gradient between arterial and end-tidal carbon dioxide [7]. The diagnostic value of this consideration has been evaluated for acute thromboembolism and was found to be fairly useful [8, 9].

We hypothesised that the capillary to end-tidal carbon dioxide gradient at rest and during exercise would provide a distinction between

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CTEPH and IPAH. We compared two groups of extensively diagnosed patients with comparable haemodynamics who, after extensive work-up, had unequivocal diagnoses of either CTEPH or IPAH, and found that both resting and maximal exercise capillary to end-tidal carbon dioxide gradients may help discriminate between these two diseases. Additionally, we described a matched control group to demonstrate the physiological range of the evaluated parameters.

METHODS

Study objectives

The objectives of the present study were to assess the typical features of ventilatory and gas exchange parameters in patients with CTEPH compared with IPAH using a cardiopulmonary exercise test with capillary blood gas analysis.

Subjects

For this study, 561 spiroergometry examinations were screened for individuals with a full diagnostic work-up and an unequivocal diagnosis of either CTEPH or IPAH. All investigations were performed in the pulmonary hypertension clinic of the Justus-Liebig University (Giessen, Germany).

The complete work-up consisted of medical history, physical examination, ECG, pulmonary function test including diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$), chest radiography, blood gas analysis, routine laboratory tests, testing for antinuclear antibodies, abdominal ultrasonography, echocardiography, ventilation/perfusion scan, pulmonary angiography and computed tomography (CT), cardiopulmonary exercise testing, and right heart catheterisation. Patients with a resting pulmonary arterial pressure of <25 mmHg, pulmonary arterial wedge pressure of >15 mmHg, forced vital capacity (FVC) <70% predicted and forced expiratory volume in 1 s (FEV_1) <70% predicted, as well as all patients with left-to-right shunt, portopulmonary hypertension, renal impairment and other associated forms of pulmonary hypertension were excluded. In addition, all patients with any significant left heart or valve disease, lung disease, systemic disease or pulmonary veno-occlusive disease, and all patients in New York Heart Association functional class IV were excluded from the study. Controls were sex- and age-matched to the patients, and were investigated with the same spiroergometry protocol and pulmonary function test. All subjects gave written informed consent for all investigations. The protocol was approved by the local ethics committee (Justus-Liebig University).

Radiographic analysis

Pulmonary angiography was performed in 15 out of the 16 CTEPH patients and in 13 out of the 21 IPAH patients, showing a positive result for pulmonary thromboembolism in all CTEPH patients, and a negative result in all IPAH patients. All patients underwent ventilation/perfusion scans. This showed a high probability of thromboembolism due to typical perfusion defects in all patients with CTEPH and a negative result (*i.e.* a low or medium probability) in all patients with IPAH. Spiral and thin-slice CT were performed in 12 out of the 16 CTEPH patients, demonstrating mosaic-like ground-glass opacities and pulmonary arterial occlusions in all of the 12 CTEPH patients; none of the IPAH patients showed a mosaic pattern or any occlusion.

Pulmonary function test

Spirometry and body plethysmography were performed with a constant volume body plethysmograph (Masterlab Body Pro; Jaeger, Höchberg, Germany). Vital capacity, FVC, FEV_1, total lung capacity, residual volume, airway resistance and $D_{L,CO}$ were determined by standard procedures. All measurements conformed to the guidelines of the European Coal and Steel Community [10], and for each individual, data are presented as % predicted values or upper limits of normal.

Right heart catheterisation

All patients underwent diagnostic right heart catheterisation within 6 weeks of spiroergometry. Baseline haemodynamic variables, including mean pulmonary arterial pressure, mean right atrial pressure, pulmonary capillary wedge pressure and mean systemic arterial pressure, were measured. Cardiac output was measured by thermodilution (catheter Type 95 F 754 H; Baxter, Deerfield, IL, USA).

Cardiopulmonary exercise testing

We applied a stepwise incremental maximal exercise test with continuous monitoring of expiratory gases and repeated blood gas analysis. Exercise was symptom-limited or stopped after objective withdrawal criteria were met. Exercise on a cycle ergometer (Spiroergometer Vmax 2130 V6200; Sensormedics BV, Houten, the Netherlands) was started with no load and stepwise increments of 30 W every 2 min up to 150 W, then with increments of 50 W every 2 min. The expiratory fractions of oxygen and carbon dioxide (F_{E,O_2} and F_{E,CO_2}, respectively), minute ventilation (V'_E), breathing frequency, temperature and air pressure were recorded continuously *via* a mouthpiece. 30-s means were calculated for tidal volume, oxygen uptake and carbon dioxide production (V'_{CO_2}). Heart rate was derived from R–R intervals and synchronised to ventilatory parameters for calculation of 30-s means. Blood pressure was measured with an arm cuff. The ventilatory equivalent for carbon dioxide (EQ_{CO_2}) was continuously calculated and 30-s means were evaluated. The EQ_{CO_2} value at the ventilatory equivalent for oxygen (EQ_{O_2}) nadir was considered as EQ_{CO_2} at the anaerobic threshold [11].

Capillary to end-tidal carbon dioxide gradient

The end-tidal carbon dioxide tension (P_{ET,CO_2}) was registered breath by breath and 30-s means were used as an estimate of the carbon dioxide tension (P_{CO_2}) of the ventilated alveolar regions. Blood gas analysis was performed from arterialised capillary blood at rest and during maximal exercise. For this purpose, blood was obtained from the earlobe at least 5 min after lubrication with Finalgon® (Boehringer Ingelheim, Ingelheim, Germany), an ointment enhancing the local blood flow, and immediately inserted into a blood gas analyser (ABL 510 Radiometer Copenhagen; Radiometer A/S, Copenhagen, Denmark). Capillary blood carbon dioxide tension was used as an estimate of arterial carbon dioxide tension. Its difference from P_{ET,CO_2} served as an estimate of the arterial to end-tidal carbon dioxide gradient, a measure introduced into clinical practice by ROBIN *et al*. [12]. Dead space ventilation (V'_D) was calculated from the Bohr formula as $V'_D = V'_E - V'_A$, and $V'_{CO_2} = F_{E,CO_2} \times V'_E$ and $V'_{CO_2} = F_{A,CO_2} \times V'_A$, where V'_A is alveolar ventilation and F_{A,CO_2} is the alveolar carbon dioxide fraction of the perfused lung regions, estimated from capillary P_{CO_2} as F_{A,CO_2} = capillary P_{CO_2}/barometric pressure.

Statistical analysis

Data were analysed using the SPSS statistical package (SPSS version 18.0; SPSS Inc., Chicago, IL, USA). The groups were tested for statistical significance using Kruskal–Wallis ANOVA. Additionally, we employed the Mann–Whitney–Wilcoxon test for comparison of the IPAH with the CTEPH group, and the control group with both patient groups. Bonferroni correction was applied where multiple testing was performed. Anthropometric and spiroergometric data, haemodynamics and pulmonary function tests are presented as median (range). Pulmonary function tests, haemodynamics and EQ_{CO_2} at the anaerobic threshold were correlated with maximal oxygen uptake ($V'_{O_2,max}$) by linear regression analysis. For assessment of the utility of capillary to end-tidal carbon dioxide gradients for prediction of CTEPH, receiver operating characteristic curves were generated. A p-value of <0.05 was considered significant.

RESULTS

21 IPAH and 16 CTEPH patients were included in the study. The mean age was similar between the two groups but the female/male ratio was higher in the IPAH than in the CTEPH group. The control group was age- and sex-matched (table 1).

Right heart catheterisation revealed that pulmonary pressure and resistance in IPAH and CTEPH were comparable, while right atrial pressure was significantly higher in the CTEPH group (table 2).

Both IPAH and CTEPH patients presented with reduced FEV_1 and reduced vital capacity compared with the control group, and CTEPH patients were significantly more affected than IPAH patients. $D_{L,CO}$ was not significantly reduced in IPAH or CTEPH (table 3).

Breathing frequency was significantly increased in CTEPH *versus* IPAH at rest and during exercise (median (range) 20 (10–27) *versus* 16 (8–26) ($p<0.05$) and 31 (27–44) *versus* 26 (18–37) breaths·min^{-1} ($p<0.001$)). Ventilation was slightly increased in CTEPH at rest and during exercise (15 (4–21) *versus* 11 (7–18) and 58 (29–78) *versus* 50 (29–82) L·min^{-1}), but with no significant difference between the two groups. There were no significant differences between CTEPH and IPAH in oxygen uptake upon maximal exercise (table 3), and tidal volume at rest and at maximal exercise (0.7 (0.4–1.3) *versus* 0.7 (0.5–1.4) and 1.9 (0.7–2.3) *versus* 1.9 (1.3–3.1) L, respectively). EQ_{CO_2} at the anaerobic threshold was significantly correlated with $V'_{O_2,max}$ in IPAH patients, while there was no such correlation in the CTEPH group (fig. 1). When CTEPH patients were compared with IPAH patients, expiratory gas analysis and capillary blood gas analysis at rest and upon maximal exercise demonstrated significantly lower P_{ET,CO_2} and, correspondingly, both patient groups showed significantly decreased capillary to end-tidal carbon dioxide gradients. Alveolar dead spaces were lowest in controls compared with patients, and they were significantly increased in CTEPH *versus* IPAH at rest and during exercise (table 4).

Within the patient groups, a resting capillary to end-tidal carbon dioxide gradient of >7.0 mmHg was indicative of CTEPH, with a sensitivity of 75% and a specificity of 95%. A resting capillary to end-tidal carbon dioxide gradient threshold of >6.3 mmHg would increase the sensitivity to 80% but decrease the specificity to 75%. An exercise capillary to end-tidal carbon dioxide gradient of >7.0 mmHg would indicate CTEPH with a specificity of 90% and a sensitivity of 88% (fig. 2).

TABLE 1 Anthropometric data

	IPAH	CTEPH	Control
Patients	21	16	37
Females/males	15/6	7/9	22/15
Age yrs	48 (32–61)	55 (32–71)	51 (32–68)
Height cm	166 (156–188)	170 (162–197)	170 (150–195)
Weight kg	75 (45–103)	73 (58–122)	67 (53–95)

Data are presented as n or median (range). IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.

DISCUSSION

This study showed that markedly increased capillary to end-tidal carbon dioxide gradients indicating heterogeneous pulmonary perfusion may help to distinguish CTEPH from IPAH. While IPAH is subject to treatment with targeted pulmonary arterial hypertension therapies, the therapy of choice for CTEPH is pulmonary endarterectomy, and early anticoagulation may prevent the development of the full disease [4, 13]. Additionally, CTEPH necessitates permanent and aggressive anticoagulation to prevent further embolic events; hence, early diagnosis is of the utmost importance.

Spiroergometry has a place in the work-up of pulmonary hypertension as it helps to define the exercise-limiting factors of an individual with pulmonary hypertension and quantifies the limitation in comparison with healthy individuals. The most important parameters are considered to be $V'_{O_2,max}$ and EQ_{CO_2} at the anaerobic threshold [14], and it has been shown that $V'_{O_2,max}$ has prognostic relevance in IPAH [15]. Our data suggest that spiroergometry also indicates whether pulmonary blood flow is heterogeneous in comparison to ventilation. Heterogeneous pulmonary perfusion is the hallmark of CTEPH. Correspondingly, this investigation indicated that CTEPH patients may be distinguished from IPAH patients based on analysis of capillary and end-tidal carbon dioxide tensions, and that a markedly increased capillary to end-tidal carbon dioxide gradient may predict CTEPH.

The arterial to end-tidal carbon dioxide gradient has been evaluated as a screening tool for the diagnosis of acute pulmonary thromboembolism. Despite some limitations, such as unselected patients, and a study population with considerable comorbidities, the combination of a negative whole blood agglutination D-dimer assay plus a normal gradient was associated with a probability of pulmonary thromboembolism <1% [8]. To our knowledge, a similar approach has not been taken for CTEPH.

Our study used a highly selected group of patients in whom pulmonary shunting, portal hypertension, lung fibrosis, chronic obstructive pulmonary disease and left heart disease had been rigorously excluded. Consequently, our results may not be applicable to an unselected patient population. We were able to show, however, that assessment of capillary to end-tidal carbon dioxide gradients at rest and during exercise may be a valuable tool to raise the suspicion level for CTEPH, especially if the

TABLE 2 Haemodynamics at rest

Parameter	IPAH	CTEPH	Correlation with $V'_{O_2,max}$ % pred	
			IPAH	CTEPH
$\bar{P}_{pa}$ mmHg	45 (31–71)	48 (33–62)	-0.55**	-0.31
CO L·min^{-1}	3.6 (2.0–5.4)	3.7 (2.3–6.7)	0.37	0.11
PVR dyn·s·cm^{-5}	936 (385–2290)	985 (372–1420)	-0.4	0.05
P_{ra} mmHg	3 (0–19)	12 (3–22)$^{\#\#}$	-0.59**	0.11
$\bar{P}_{sa}$ mmHg	91 (50–116)	95 (66–131)	0.08	0.15
SVR dyn·s· cm^{-5}	1828 (1110–2593)	2091 (811–3166)	-0.05	-0.06
S_{a,O_2} %	94 (80–99)	93 (84–100)	0.54*	0.27
S_{v,O_2} %	68 (34–74)	53 (34–75)	0.62**	0.31
CI L·min^{-1}·m^{-2}	2.0 (1.3–3.1)	1.8 (1.3–3.8)	0.44*	0.43

Data are presented as median (range) or correlation coefficient. IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; $V'_{O_2,max}$: maximal oxygen uptake; % pred: % predicted; $\bar{P}_{pa}$: mean pulmonary arterial pressure; CO: cardiac output; PVR: pulmonary vascular resistance; P_{ra}: right atrial pressure; $\bar{P}_{sa}$: mean systemic arterial pressure; SVR: systemic vascular resistance; S_{a,O_2}: arterial oxygen saturation; S_{v,O_2}: mixed venous oxygen saturation; CI: cardiac index. $^{\#\#}$: $p<0.01$ for difference between IPAH and CTEPH; *: $p<0.05$ for correlation with $V'_{O_2,max}$; **: $p<0.01$ for correlation with $V'_{O_2,max}$.

confounding diseases listed above have been excluded. The study showed that both increased resting and exercise capillary to end-tidal carbon dioxide gradients indicated CTEPH. The sensitivity and specificity, however, favoured the exercise data for the differentiation from IPAH. With a detection threshold set at a capillary to end-tidal carbon dioxide gradient of >7.0 mmHg, the sensitivity for detection of CTEPH was 75% at rest and 88% during exercise. Assessment of capillary to end-tidal carbon dioxide gradient, which is easy to measure, might therefore allow earlier initiation of further diagnostic tests for thromboembolic disease.

We also analysed EQ_{CO_2} at the anaerobic threshold. This parameter corresponds closely to the V'_E/V'_{CO_2} slope at the anaerobic threshold [12]. We found that in IPAH patients, EQ_{CO_2} was inversely correlated with $V'_{O_2,max}$. This can be explained by the fact that reduced pulmonary blood flow results in both a reduced $V'_{O_2,max}$ and an increased V'_E/V'_{CO_2} ratio [14, 16]. Interestingly, in the CTEPH group, there was no significant correlation between EQ_{CO_2} and $V'_{O_2,max}$. This might be explained by the fact that blood flow heterogeneity through the lung is influenced by two different factors: the extent of vascular occlusion and the tone of the nonoccluded vessels. If, for example, 50% of the vessels are occluded and 50% are completely normal, the nonoccluded vessels are largely hyperperfused, the pulmonary arterial pressure is normal and the heterogeneous blood flow accounts for a highly increased EQ_{CO_2}. Indeed, with progressive disease, the nonoccluded vessels tend to narrow due to remodelling of the small pulmonary arteries [17]; this reduces the extent of blood flow heterogeneity and, thereby, decreases EQ_{CO_2} but also results in a decrease in $V'_{O_2,max}$, precluding an inverse correlation of these parameters. Resting haemodynamics showed a significant correlation with $V'_{O_2,max}$. This was an expected finding, because the degree of pulmonary vascular obliteration limits maximal cardiac output. Interestingly, correlation coefficients were generally higher in the IPAH than the CTEPH group. This could also be due to the heterogeneity of pulmonary blood flow in CTEPH patients that may contribute to exercise limitation apart from pulmonary haemodynamics.

TABLE 3 Pulmonary function test, capillary oxygen tension (P_{c,O_2}) and maximal oxygen uptake ($V'_{O_2,max}$)

Parameter	Control	IPAH	CTEPH	ANOVA p-value
Subjects n	37	21	16	
FEV_1 % pred	100 (85–127)	94 (70–108)*,$^{\#}$	77 (56–107)*	<0.001
VC % pred	99 (85–120)	94 (70–114)$^{\#}$	81 (56–110)***	<0.001
TLC % pred	113 (95–130)	101 (82–120)**	96 (69–134)	0.01
Resistance % ULN	71 (41–100)	93 (45–159)*	88 (46–149)*	0.002
$D_{L,CO}$ % pred	99 (67–113)	73 (28–111)**	67 (52–114)**	<0.001
P_{c,O_2} mmHg	80 (66–105)	69 (46–93)**	62 (49–86)**	<0.001
$V'_{O_2,max}$ % pred	97 (75–169)	52 (27–88)***	42 (28–65)***	<0.001

Data are presented as median (range), unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; VC: vital capacity; TLC: total lung capacity; ULN: upper limit of normal; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. *: $p<0.05$ for difference from control; **: $p<0.01$ for difference from control; ***: $p<0.001$ for difference from control; $^{\#}$: $p<0.05$ for difference between IPAH and CTEPH.

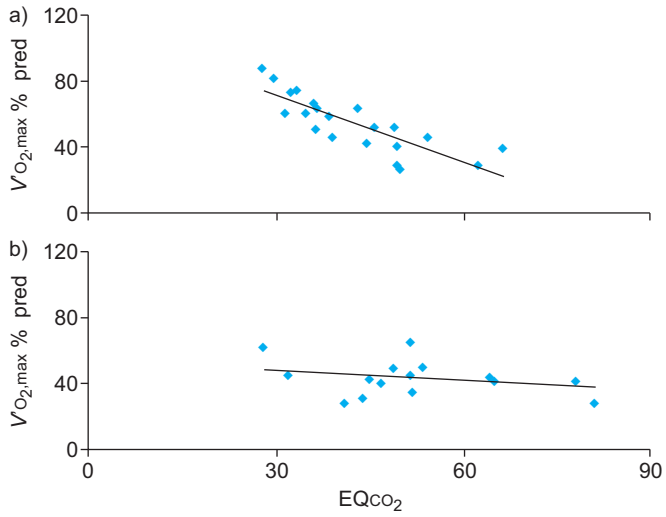

FIGURE 1. Correlation of maximal oxygen uptake ($V'_{O_2,max}$) with ventilatory equivalent for carbon dioxide (EQ_{CO_2}) in a) idiopathic pulmonary arterial hypertension (r= -0.815, $p=6.69 \times 10^{-6}$) and b) chronic thromboembolic pulmonary hypertension (r= -0.316, p=0.234) patients. % pred: % predicted.

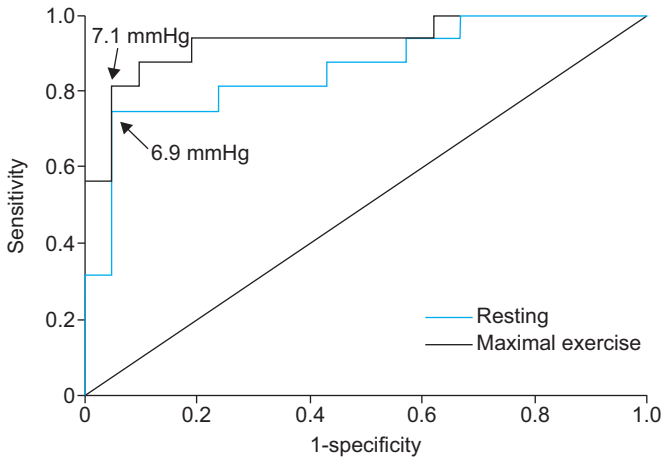

FIGURE 2. Receiver operating characteristic curve for the determination of chronic thromboembolic pulmonary hypertension. Capillary to end-tidal carbon dioxide gradient.

Ventilatory inefficiency in PAH and CTEPH is associated with hyperventilation. This may be due to increased chemosensitivity [18] or an augmented dead space fraction [19]. ZHAI *et al*. [19] investigated ventilatory efficiency by comparing physiological dead space fraction and EQ_{CO_2} in PAH and CTEPH patients. These data suggested a greater dead space in CTEPH compared with PAH, explaining the pronounced ventilatory inefficiency in CTEPH, which is in agreement with our results. In contrast to ZHAI *et al*. [19], we additionally evaluated capillary to end-tidal carbon dioxide gradients and found that for diagnostic purposes, they may be easier to use than calculated dead space fractions. Because EQ_{CO_2} values in both IPAH and CTEPH were consistent with capillary P_{CO_2}, and dead spaces were increased in CTEPH and IPAH, we conclude that both increased chemosensitivity and increased dead space fraction contribute to ventilatory inefficiency in IPAH and CTEPH, which is in agreement with NAEIJE and VAN DE BORNE [20].

Our study has some limitations, such as the small number of patients, the retrospective design and the fact that our population was highly selected. This selection allowed us to highlight the specific differences between IPAH and CTEPH, promoting earlier detection of patients with CTEPH; the results, however, may not be applicable to an unselected population of pulmonary hypertension patients. Prospective studies and studies in a more general population of patients with pulmonary hypertension are warranted in order to evaluate the utility of capillary or arterial to end-tidal carbon dioxide gradients in a diagnostic algorithm.

Undoubtedly, a CT-angiogram or pulmonary angiogram will always be necessary to determine operability in case of CTEPH. However, noninvasive methods raising the suspicion of CTEPH

TABLE 4 Capillary carbon dioxide tension (P_{c,CO_2}) and expiratory gases at rest and during maximal exercise

Parameter	Rest				Maximal exercise			
	Control	IPAH	CTEPH	ANOVA p-value	Control	IPAH	CTEPH	ANOVA p-value
Subjects n	37	21	16		37	21	16	
P_{c,CO_2} mmHg	38.1 (32.0–42.1)	31.7$^{\#\#\#}$ (24.1–37.6)	32.8$^{\#\#\#}$ (27.1–38.2)	<0.001	37.5 (27.4–44.2)	31.6$^{\#\#\#}$ (22.8–39.0)	29.5$^{\#\#\#}$ (22.8–40.7)	<0.001
P_{ET,CO_2} mmHg	35.8 (26.5–44.7)	27.2$^{*,\#\#\#}$ (20.4–35.0)	22.7$^{\#\#\#}$ (20.3–35.1)	<0.001	39.4 (26.3–48.3)	28.3$^{**,\#\#\#}$ (16.5–38.9)	19.7$^{\#\#\#}$ (13.8–34.0)	<0.001
$P_{c\text{-}ET,CO_2}$ mmHg	2.3 (-4.8–8.1)	4.4*** (0.9–9.0)	8.6$^{\#\#\#}$ (3.0–13.7)	<0.001	-1.9 (-5.7–6.2)	4.1$^{***,\#\#\#}$ (0.0–8.8)	9.3$^{\#\#\#}$ (3.3–13.1)	<0.001
V_D/V_T %	42 (13–64)	46** (29–61)	58$^{\#\#\#}$ (39–66)	<0.001	23 (5–51)	35$^{***,\#\#\#}$ (19–52)	49$^{\#\#\#}$ (29–57)	<0.001

Data are presented as median (range), unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; P_{ET,CO_2}: end-tidal carbon dioxide tension; $P_{c\text{-}ET,CO_2}$: capillary to end-tidal carbon dioxide gradient ($P_{c,CO_2} - P_{ET,CO_2}$); V_D: dead space volume (calculated according to Bohr's formula); V_T: tidal volume. $^{\#\#\#}$: p<0.001 for difference from control; *: p<0.05 for difference between IPAH and CTEPH; **: p<0.01 for difference between IPAH and CTEPH; ***: p<0.001 for difference between IPAH and CTEPH.

may be valuable as screening tools for patients with thromboembolic diseases. Spiroergometry is a widely used method in patients with dyspnoea, and the detection of gas-exchange abnormalities indicative of a thromboembolic disease may guide the establishment of priorities for further diagnostics and therapy. This might be considered as the true clinical utility of this work.

Conclusion

Spiroergometry with repeated blood gas analysis may distinguish CTEPH patients from IPAH patients based on increased capillary to end-tidal carbon dioxide gradients at rest and during exercise.

STATEMENT OF INTEREST

None declared.

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