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# Dead-space ventilation is linked to exercise capacity and survival in distal chronic thromboembolic pulmonary hypertension



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## KEYWORDS:

cardiopulmonary  
exercise test;  
chronic thromboem-  
bolic disease;  
physiologic dead  
space;  
pulmonary artery  
hypertension;  
ventilatory efficiency;  
gas exchange

**BACKGROUND:** Cardiopulmonary exercise testing (CPET) is frequently used for the evaluation of patients with pulmonary hypertension (PH). Non-operable distal chronic thromboembolic pulmonary hypertension (CTEPH) represents a unique subgroup of PH where microvascular disease resembling pulmonary arterial hypertension (PAH) may predominate and efficacious medical therapy is now available. However, little is known regarding the detailed CPET profile of patients with distal CTEPH, and whether ventilation and gas exchange responses are different from PAH.

**METHODS:** Forty-nine consecutive patients with non-operable distal CTEPH according to multidisciplinary team assessment and 45 PAH patients underwent CPET and right heart catheterization. Patients were followed up for a median of 3.2 years (interquartile range: 1.8 to 4.4).

**RESULTS:** Pulmonary hemodynamics were similar in distal CTEPH and PAH groups, but patients with distal CTEPH achieved a lower percent predicted peak oxygen consumption ( $59 \pm 13\%$  vs  $66 \pm 14\%$ ,  $p < 0.05$ ). At peak exercise, higher physiologic dead-space fraction (VD/VT) ( $0.45 \pm 0.07$  vs  $0.35 \pm 0.07$ ,  $p < 0.0001$ ) and higher arterial-to-end-tidal carbon dioxide gradient ( $9 \pm 3$  vs  $5 \pm 3$  mm Hg,  $p < 0.0001$ ) were observed in distal CTEPH compared with PAH. Ventilatory efficiency, expressed as VE/VCO<sub>2</sub> slope, was also more impaired in distal

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CTEPH ( $52.2 \pm 10.1$  vs  $43.8 \pm 8.4$  liters/min,  $p < 0.0001$ ). In the distal CTEPH group only, higher VD/VT was associated with lower peak oxygen consumption ( $r = -0.46$ ,  $p = 0.003$ ) and worse survival.

**CONCLUSIONS:** Compared with PAH, a distinct pattern of response to exercise was observed in distal CTEPH, characterized by increased dead-space ventilation that resulted in worse ventilatory efficiency and greater impairment of exercise capacity. In distal CTEPH, dead-space ventilation correlated with exercise capacity and was associated with survival.

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Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) of  $\geq 25$  mm Hg<sup>1</sup> and is associated with increased morbidity and mortality, regardless of the underlying etiology.<sup>2</sup> Exercise impairment is a major feature of PH, and cardiopulmonary exercise testing (CPET) is used widely in clinical practice as an objective measure of exercise capacity and as a prognostic tool.<sup>3</sup>

Chronic thromboembolic PH (CTEPH) is a form of PH caused by persistence of thrombotic material in the pulmonary arterial bed despite therapeutic anticoagulation.<sup>4</sup> The diagnosis of CTEPH is based on the presence of PH established by right heart catheterization (RHC), perfusion defects on ventilation–perfusion scan and obstructive arterial lesions on pulmonary angiography.<sup>5</sup> From a management perspective, CTEPH is divided into either proximal (technically operable) or distal (non-operable) forms of disease, with the proximal form involving mainly the large elastic vessels to the segmental artery level, and the distal form with lesions that reside predominantly beyond the segmental level.<sup>5–7</sup> Moreover, CTEPH patients also have involvement of the distal pulmonary arteries,<sup>8,9</sup> as seen in pulmonary arterial hypertension (PAH).

The pathophysiology of the proximal form of CTEPH has been studied widely, but there exists limited information regarding cardiopulmonary response during exercise in the distal form of the disease. Previous studies have shown that CTEPH patients display greater impairment of ventilatory efficiency and more pronounced gas exchange abnormalities compared with PAH patients.<sup>10</sup> These features can be explained, in part, by the increased dead-space ventilation (VD/VT) that occurs in CTEPH. To our knowledge, it has never been specifically addressed as to whether CTEPH with distal disease displays a specific profile, and thus we reasoned that it would be useful to characterize the cardiopulmonary response in the non-operable form of CTEPH. Our aim in this study was to compare the physiologic profile during CPET in patients with distal CTEPH against a comparable population of PAH patients in terms of age and anthropometric data. We hypothesized that patients with distal CTEPH would display higher ventilatory inefficiency and greater gas exchange abnormalities during exercise. We further hypothesized that dead-space ventilation would be linked to impairment of exercise capacity in distal CTEPH but not in PAH. Because patients with distal CTEPH do not undergo surgery, we aimed to determine

whether the severity of dead-space ventilation would be associated with prognosis.

## Methods

### Population

Forty-nine consecutive and clinically stable patients with distal CTEPH, referred to the French Reference Center for Severe Pulmonary Hypertension (Le Kremlin-Bicêtre, France) for management of distal CTEPH between 2010 and 2014, were included in this retrospective study. Diagnosis of CTEPH was made according to guideline recommendations,<sup>5</sup> and the classification of distal (non-operable) CTEPH was based on multidisciplinary consensus involving pulmonologists, radiologists and surgeons after review of all available clinical information, as described elsewhere.<sup>7</sup> Subjects with thrombotic lesions accessible to surgery but considered inoperable for pulmonary endarterectomy (PEA) due to comorbid medical conditions were excluded. Forty-five clinically stable patients with a diagnosis of idiopathic, heritable or anorexigen-induced PAH and without other significant concomitant diseases were also evaluated over the same period. PAH patients with positive acute vasoreactivity to nitric oxide were excluded to avoid potential selection of subjects with normalization of hemodynamics after calcium channel blocker therapy. The demographic and hemodynamic characteristics of the patients were extracted from the French National Registry for PH. Subjects were matched for gender, height and age (refer to [Supplementary Material](#) available online at [www.jhltonline.org/](http://www.jhltonline.org/)). Subjects recruited provided informed consent for the use of their clinical data, and the registry was established in accordance with French bioethics law (Commission Nationale de l'Informatique et des Libertés, No. 842063).

### Right heart catheterization

Hemodynamic evaluation was performed at rest in the supine position. The zero-level reference was determined at the mid-thoracic line. RHC was performed using the modified Seldinger technique with an 8F sheath inserted in the jugular, basilic or cephalic vein. The Swan–Ganz catheter used was a 7F, 2-lumen, fluid-filled, pressure-measuring tipped catheter (Corodyn TD; Braun Medical, Bethlehem, PA). CPET and RHC were performed in the same week.

### Cardiopulmonary exercise test

All CPET were performed using incremental symptom-limited cycle ergometer exercise with breath-by-breath measurements of

oxygen consumption ( $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ) and ventilation (VE). Heart rate (HR) and systemic blood pressure were monitored during the test. Blood gases for arterial partial pressure of oxygen ( $\text{PaO}_2$ ) and carbon dioxide ( $\text{PaCO}_2$ ) at rest and at peak exercise were obtained by radial artery puncture in the majority of subjects studied ( $n = 40$  distal CTEPH,  $n = 43$  PAH). Other variables derived from CPET included  $\text{VE}/\text{VO}_2$ ,  $\text{VE}/\text{VCO}_2$  (ratio and slope), oxygen pulse ( $\text{VO}_2/\text{HR}$ ), partial pressure of end-tidal carbon dioxide ( $\text{PETCO}_2$ ), physiologic dead-space fraction ( $\text{VD}/\text{VT}$ ), alveolar arterial gradient for oxygen  $[(\text{A}-\text{a})\text{O}_2]$  and arterial to end-tidal carbon dioxide tension gradient  $[(\text{a}-\text{ET})\text{CO}_2]$ .  $\text{VD}/\text{VT}$  was calculated according to the Enghoff modification of the Bohr dead-space equation.<sup>11</sup>

## Statistical analysis

Data are presented as mean and standard deviation, unless stated otherwise. Comparisons were made using an unpaired *t*-test or Mann–Whitney test as appropriate, according to the distribution of data. Statistically significant differences between New York Heart Association (NYHA) functional class (FC), gender distribution and between-group treatment were evaluated by chi-square test with Yates correction. Correlations were assessed by Pearson's or Spearman's coefficient of correlation, as appropriate. Multivariate analyses were performed using a stepwise multiple regression model for  $\text{VO}_2$  and stepwise logistic regression for NYHA FC. Our model included mPAP, cardiac output (CO), number of specific PAH therapies, and peak exercise  $\text{VD}/\text{VT}$ . Comparison of Kaplan–Meier survival curves was performed and survival comparisons were made using the log-rank test. Statistical significance was set at  $p < 0.05$ . Statistical analyses were performed using MEDCALC for Windows, version 12.5 (MedCalc Software, Ostend, Belgium).

## Results

### Study subjects

Baseline patient characteristics are provided in Table 1. The distal CTEPH and PAH groups were not significantly different with regard to age, gender, anthropometrics, lung function parameters or resting hemodynamics. NYHA FC was different between the 2 groups with more severe functional impairment in distal CTEPH ( $p = 0.015$ ). A higher rate of triple therapy was employed in the PAH group and there were more untreated patients in the distal CTEPH group at the time of CPET ( $p < 0.001$ ).

### Exercise capacity

All subjects reached anaerobic threshold (AT) with a high respiratory exchange ratio (RER) and a significant rise in blood lactate at peak exercise, consistent with heavy exercise. Peak  $\text{VO}_2$  was slightly lower in the distal CTEPH group compared with the PAH group ( $59 \pm 13$  vs  $66 \pm 14$  percent predicted,  $p = 0.013$ ). Workload, HR and oxygen pulse achieved at peak exercise were not significantly different between the groups (Table 2).

**Table 1** Demographic and Hemodynamic Results

	Distal CTEPH ( $n = 49$ )	PAH ( $n = 45$ )	<i>p</i> -value
Age (years)	$56.1 \pm 13.1$	$52.0 \pm 10.4$	0.10
Gender female (%)	51	69	0.14
Height (m)	$1.68 \pm 0.11$	$1.65 \pm 0.09$	0.13
Weight (kg)	$73.4 \pm 17.1$	$72.3 \pm 14.6$	0.87
FEV <sub>1</sub> (% pred)	$92 \pm 19$	$89 \pm 17$	0.49
FVC (% pred)	$102 \pm 21$	$101 \pm 19$	0.84
DLCO (% pred)	$67 \pm 17$	$65 \pm 14$	0.44
NYHA	14/47/39	13/73/13	0.015
Class I/II/III (%)			
BNP (pg/ml)	$62$ (17 to 135) <sup>a</sup>	$27$ (14 to 91) <sup>a</sup>	0.12
6MWD (m)	$473 \pm 72$	$496 \pm 87$	0.17
mPAP (mm Hg)	$39 \pm 11$	$40 \pm 11$	0.70
CO (liters/min)	$5.3 \pm 1.3$	$5.8 \pm 1.1$	0.06
PVR (WU)	$6.2 \pm 3.0$	$5.6 \pm 2.2$	0.35
PAWP (mm Hg)	$8 \pm 3$	$8 \pm 3$	0.80
RAP (mm Hg)	$6 \pm 3$	$5 \pm 4$	0.65
Specific PAH therapies [ <i>n</i> (%)]			
No treatment	20 (41)	5 (11)	<0.001
Monotherapy	8 (16)	12 (27)	
Double therapy	19 (39)	13 (29)	
Triple therapy	2 (4)	15 (33)	

Data are expressed as mean  $\pm$  standard deviation, or as noted otherwise. 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; CO, cardiac output; DLCO, diffusing capacity or transfer factor of the lung for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WU, Wood units; % pred, percentage of predicted.

<sup>a</sup>Median (interquartile range).

### Ventilatory response during exercise

At rest and at peak exercise, respiratory rate (RR) was similar in the 2 groups, but resting and peak tidal volume (VT) levels were significantly increased in the distal CTEPH group compared with the PAH group (Table 2). VE at peak exercise was also significantly higher in the distal CTEPH group ( $72 \pm 21$  vs  $63 \pm 17$  liters/min,  $p = 0.049$ ). Relationships between VE,  $\text{VO}_2$  and  $\text{VCO}_2$  are shown in Figure 1. In the distal CTEPH group,  $\text{VE}/\text{VCO}_2$  slope during exercise was significantly higher ( $61 \pm 18$  vs  $48 \pm 11$ ,  $p < 0.0001$ ), with a higher  $\text{VE}/\text{VCO}_2$  ratio at AT ( $52 \pm 10$  vs  $44 \pm 8$ ,  $p < 0.0001$ ), reflecting greater ventilatory inefficiency compared with PAH.

### Gas exchange and dead-space ventilation

Results of gas exchange parameters at rest and at peak exercise are given in Table 3 and Figure 2. Distal CTEPH patients displayed lower  $\text{PaO}_2$  compared with PAH patients ( $69 \pm 12$  vs  $73 \pm 11$  mm Hg,  $p = 0.037$ ), which became more pronounced at peak exercise ( $67 \pm 15$  vs  $78 \pm 14$  mm Hg,  $p < 0.0001$ ).

**Table 2** Cardiopulmonary Exercise Test Results

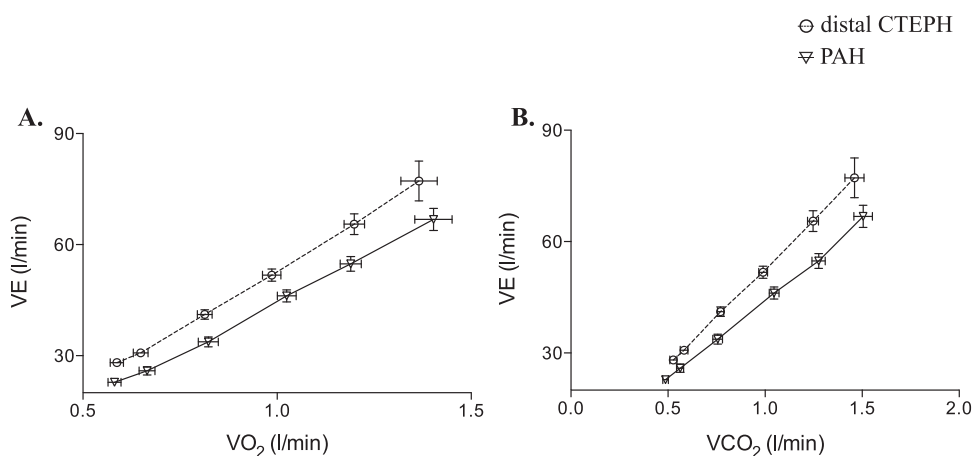
	Distal CTEPH ( <i>n</i> = 49)	PAH ( <i>n</i> = 45)	<i>p</i> -value
<b>Resting</b>			
VT (liters)	0.88 (0.67 to 1.09) <sup>a</sup>	0.74 (0.56 to 0.87) <sup>a</sup>	0.016
RR (/min)	18.4 ± 8.2	17.9 ± 5.8	0.74
<b>Anaerobic threshold</b>			
Workload (W)	44 ± 23	51 ± 21	0.16
VO <sub>2</sub> (ml/min)	871 ± 243	960 ± 272	0.10
VCO <sub>2</sub> (ml/min)	824 ± 238	923 ± 279	0.07
RER	0.96 (0.92 to 0.99) <sup>a</sup>	0.97 (0.94 to 0.99) <sup>a</sup>	0.54
HR (/min)	119 ± 19	117 ± 15	0.62
VO <sub>2</sub> /HR (ml)	7.3 ± 1.8	8.2 ± 2.3	0.03
VE (liters/min)	40.0 (34.1 to 47.9) <sup>a</sup>	38.6 (32.2 to 47.7) <sup>a</sup>	0.39
VE/VO <sub>2</sub>	49.0 (43.3 to 55.0) <sup>a</sup>	41.5 (36.0 to 46.8) <sup>a</sup>	<0.0001
VE/VCO <sub>2</sub>	51.5 (46.0 to 58.0) <sup>a</sup>	43.5 (38.0 to 49.5) <sup>a</sup>	<0.0001
<b>Peak exercise</b>			
Workload (W)	81 ± 29	82 ± 25	0.81
VO <sub>2</sub> (ml/min)	1,110 ± 332	1,188 ± 281	0.22
VO <sub>2</sub> (% pred)	59 ± 13	66 ± 14	0.013
VCO <sub>2</sub> (ml/min)	1,252 ± 378	1,357 ± 326	0.15
RER	1.13 ± 0.11	1.14 ± 0.10	0.51
HR (/min)	141 ± 19	139 ± 19	0.70
HR (% pred max)	87 ± 11	84 ± 11	0.23
VO <sub>2</sub> /HR (ml)	7.8 ± 2.2	8.8 ± 2.9	0.20
VE (liters/min)	72.0 ± 21.1	63.9 ± 7.8	0.049
VE/VO <sub>2</sub>	63.5 (54 to 73.8) <sup>a</sup>	54.5 (46.3 to 60.8) <sup>a</sup>	0.001
VE/VCO <sub>2</sub>	58.0 (49.5 to 66.3) <sup>a</sup>	46.0 (41.3 to 54.0) <sup>a</sup>	<0.0001
VT (liters)	1.88 ± 0.55	1.41 ± 0.41	0.017
BR (/min)	35.7 ± 8.9	37.1 ± 8.7	0.18
Breath reserve (%)	21 ± 17	24 ± 17	0.52
Lactate (mmol/liter)	5.7 ± 2.4	5.6 ± 1.5	0.69

Results are expressed as mean ± standard deviation, or as noted otherwise. BR, breathing rate; HR, heart rate; RER, respiratory exchange ratio; RR, respiratory rate; VCO<sub>2</sub>, carbon dioxide production; VE, ventilation; VO<sub>2</sub>, oxygen consumption; VT, tidal volume.

<sup>a</sup>Median (IQ).

Furthermore, at peak exercise, distal CTEPH patients had a higher (A-a)O<sub>2</sub> gradient compared with PAH patients (56 ± 15 vs 45 ± 15 mm Hg, *p* < 0.0001). There were no statistically significant differences for PaCO<sub>2</sub> at rest and at peak between the groups.

VD/VT at peak exercise was markedly higher in distal CTEPH patients than in PAH patients (0.45 ± 0.07 vs 0.35 ± 0.07, *p* < 0.0001), accompanied by an increased (a-ET) CO<sub>2</sub> gradient (9 ± 3 vs 5 ± 3 mm Hg, *p* < 0.0001). When the VE/VCO<sub>2</sub> ratio was plotted as a function of PaCO<sub>2</sub> at



**Figure 1** (A) Relationships between VE and VO<sub>2</sub> in distal CTEPH and PAH patients. (B) Relationship between VE and VCO<sub>2</sub> in distal CTEPH and PAH patients.

**Table 3** Gases Exchange and Derived Variables at Rest and at Peak Exercise

	Distal CTEPH (n = 40)	PAH (n = 43)	p-value
<b>Rest</b>			
PaO <sub>2</sub> (mm Hg)	68.6 ± 11.6	73.3 ± 11.4	0.037
PaCO <sub>2</sub> (mm Hg)	32.2 ± 3.0	33.0 ± 4.6	0.66
(A-a)O <sub>2</sub> (mm Hg)	43 ± 14	37 ± 13	0.0193
(a-ET)CO <sub>2</sub> (mm Hg)	9 ± 3	6 ± 3	0.001
PETCO <sub>2</sub> (mm Hg)	24 ± 4	27 ± 4	<0.001
VD/VT	0.42 ± 0.09	0.35 ± 0.08	<0.0001
<b>Peak exercise</b>			
PaO <sub>2</sub> (mm Hg)	67.0 ± 15.2	78.1 ± 13.5	<0.0001
PaCO <sub>2</sub> (mm Hg)	29.9 ± 4.1	30.3 ± 4.5	0.73
(A-a)O <sub>2</sub> (mm Hg)	56 ± 15	45 ± 15	<0.0001
(a-ET)CO <sub>2</sub> (mm Hg)	9 ± 3	5 ± 3	<0.0001
PETCO <sub>2</sub> (mm Hg)	21 ± 5	25 ± 5	<0.0001
VD/VT	0.45 ± 0.07	0.35 ± 0.07	<0.0001
ΔPaO <sub>2</sub> (mm Hg)	-1.7 ± 11.7	4.9 ± 15.3	<0.0001
ΔPaCO <sub>2</sub> (mm Hg)	-2.3 ± 3.7	-2.4 ± 3.0	0.54

Results are expressed as mean ± standard deviation. PaO<sub>2</sub>, partial pressure of oxygen in arterial blood; PaCO<sub>2</sub>, partial pressure of carbon dioxide in arterial blood; PETCO<sub>2</sub>, partial pressure of end-tidal carbon dioxide; VD/VT, physiologic dead space; (A-a)O<sub>2</sub>, alveolar-arterial gradient for oxygen; (a-ET)CO<sub>2</sub>, arterial-end-tidal carbon dioxide tension gradient.

peak exercise, the distal CTEPH group, when compared with the PAH group, displayed higher PaCO<sub>2</sub> values at an

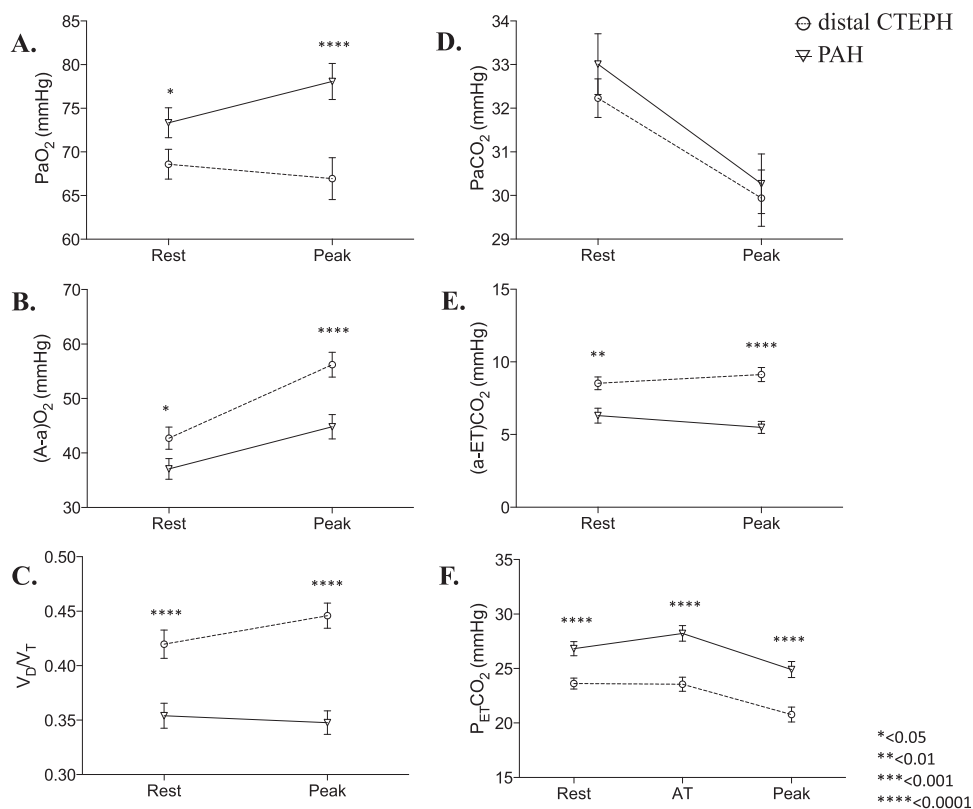
equivalent VE/VCO<sub>2</sub> level, indicative of increased dead-space ventilation (refer to Figure A1 in the Supplementary Material available online at [www.jhltonline.org/](http://www.jhltonline.org/)).

### Impact of treatment on CPET

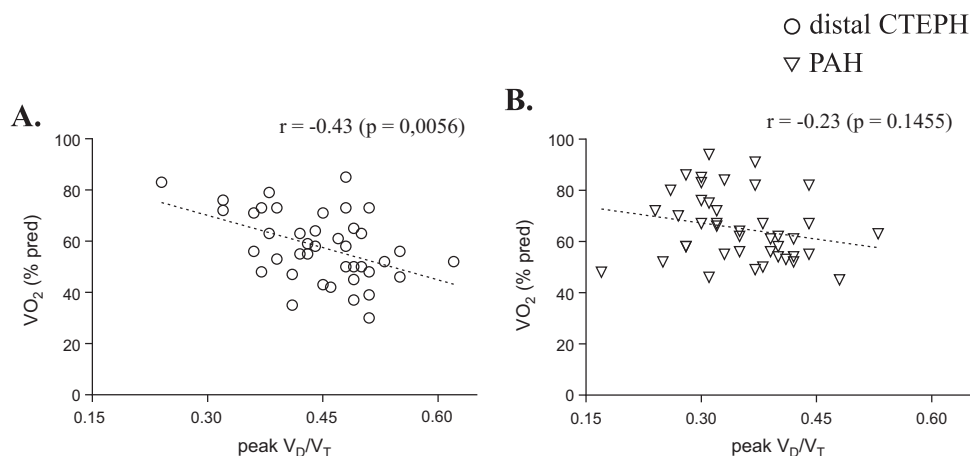
Analyses between treated patients in both groups were also performed. Distal CTEPH patients treated by specific PAH therapies displayed higher VE/VCO<sub>2</sub> ( $p = 0.0002$ ), lower peak PaO<sub>2</sub> ( $p = 0.0006$ ), higher VD/VT ( $p < 0.0001$ ) and lower VO<sub>2</sub> ( $p = 0.0375$ ) compared with treated PAH patients.

### Relationship between dead-space ventilation and exercise capacity

In the distal CTEPH group, VD/VT was inversely associated with peak VO<sub>2</sub> ( $r = -0.46$ ,  $p = 0.003$ ) (Figure 3) and more advanced NYHA FC status (VD/VT in FC I/II vs FC III:  $0.42 \pm 0.07$  vs  $0.48 \pm 0.06$ ,  $p = 0.011$ ) (Figure 4). However, no statistically significant associations were observed for the same relationships in the PAH group. Multivariate analyses showed that impaired VO<sub>2</sub> and NYHA FC were independently associated with increased peak VD/VT in distal CTEPH ( $p = 0.007$  and  $p = 0.042$ , respectively), but not in PAH, where VO<sub>2</sub> was independently determined by CO ( $p = 0.035$ ). No variable was significantly associated with NYHA FC in PAH.



**Figure 2** Evolution of gas exchange at rest and at peak exercise in distal CTEPH and PAH patients. (A) Arterial partial pressure for oxygen. (B) Alveolar-arterial gradient for oxygen. (C) Physiologic dead space. (D) Arterial partial pressure for carbon dioxide. (E) Arterial-end-tidal carbon dioxide tension gradient. (F) Partial pressure of end-tidal carbon dioxide.



**Figure 3** Correlations between  $VO_2$  percent predicted and  $VD/VT$  in both groups. (A) Distal CTEPH patients. (B) PAH patients.

### Peak $VD/VT$ association with survival in distal CTEPH

The median follow-up period of the entire population was 3.2 (1.8 to 4.4) years. Kaplan–Meier survival curves were assessed in each group according to peak  $VD/VT$  above and below the median value. Higher  $VD/VT$  (above the median) was associated with worse survival in the distal CTEPH group ( $p = 0.043$ ) but not in the PAH group ( $p = 0.084$ ) (Figure 5).

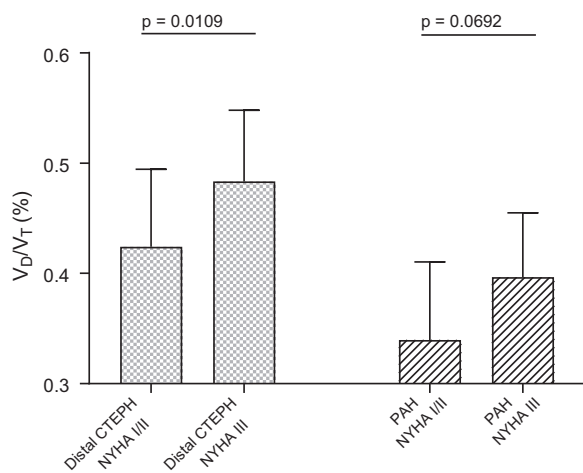
### Discussion

In this study we have demonstrated major physiologic differences in exercise profiles of patients with distal CTEPH and PAH in terms of ventilatory efficiency and gas exchange. The main results can be summarized as follows: (1) Ventilatory efficiency was more impaired in distal CTEPH with increased ventilation for a given  $CO_2$  output. This was associated with increased physiologic dead space at rest and at peak exercise when compared with PAH patients. (2) Gas exchange was more severely impaired in

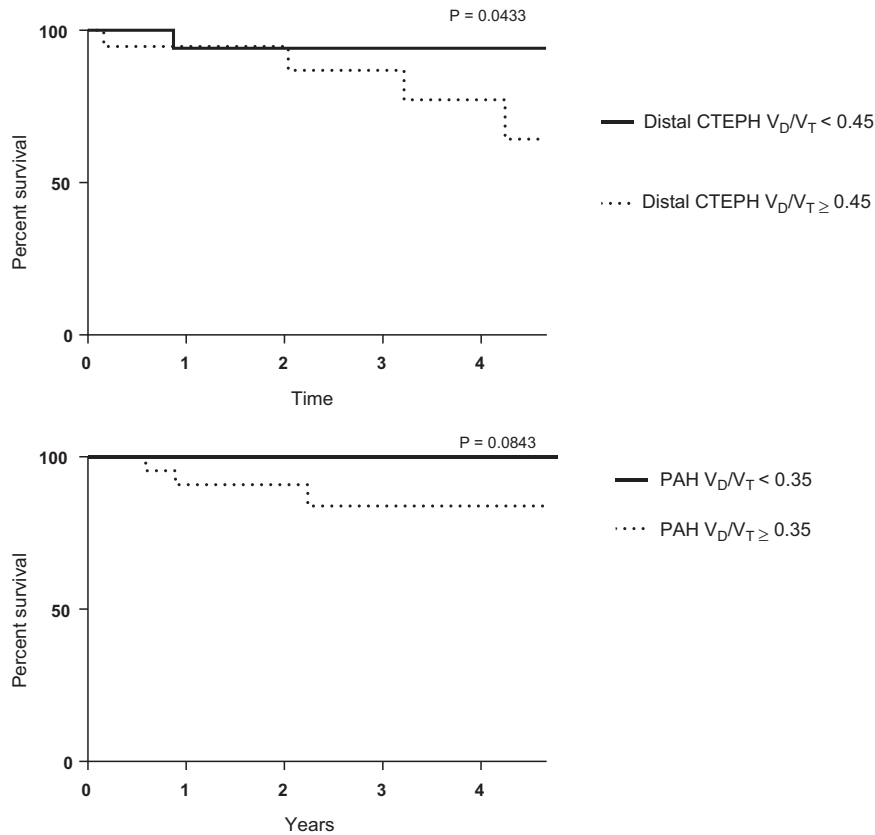
distal CTEPH at rest with a pronounced worsening at peak exercise. (3)  $VO_2$  and NYHA FC were significantly associated with peak  $VD/VT$  in distal CTEPH but not in PAH. (4) Higher peak  $VD/VT$  in distal CTEPH predicted worse survival. These findings suggest that  $VD/VT$  at peak exercise could be a specific clinical marker in distal CTEPH.

The ventilation response during exercise is complex and multifactorial. The rise in ventilation triggered by effort is determined by different physiologic variables related to cellular metabolism, such as increase in  $CO_2$  load, lactic acidosis and decreased blood oxygen content.<sup>12</sup> The adjustment of ventilation to metabolic demands during exercise can be determined by the ratio  $VE/VCO_2$  as a measure of ventilatory efficiency.<sup>13</sup> Ventilation is also associated with arterial blood oxygen content,<sup>14</sup> and acute hypoxemia during exercise contributes to the stimulation of ventilation.<sup>15</sup> The pulmonary circulation adapts during exercise to preserve gas exchange with a rise in capillary blood volume and an increase in mean  $V/Q$  relationship.<sup>16</sup> In pulmonary vascular disease, these mechanisms are altered and hypoxemia is the result of broadened  $V/Q$  distribution amplified by a lowered mixed venous oxygen content.<sup>17</sup>

Lower ventilatory efficiency is a hallmark of many cardiopulmonary diseases,<sup>18–20</sup> and ventilatory efficiency has been associated with functional impairment and worse prognosis in PAH.<sup>17,21</sup> An elevated  $VE/VCO_2$  ratio may be due to an increased physiologic dead-space fraction leading to a higher rate of ventilation to eliminate  $CO_2$ .<sup>14,18</sup> In our study,  $VE/VCO_2$ , peak exercise  $VD/VT$  and  $(a-ET)CO_2$  were significantly increased in the distal CTEPH group compared with the PAH group. Previous studies have highlighted an increased  $VD/VT$  and greater ventilation inefficiency in heterogeneous populations of CTEPH patients compared with PAH patients.<sup>10,22,23</sup> Our study extends these observations for the specific population of patients with non-operable distal CTEPH. Of interest is that, in distal CTEPH, it is believed that there is increased involvement of the small pulmonary arteries, with lesions resembling PAH.<sup>8,9</sup> However, greater impairment of ventilatory efficiency appears to be a characteristic feature of CTEPH, regardless of whether the vascular disease is



**Figure 4** Difference of  $VD/VT$  according to NYHA FC and diseases.



**Figure 5** Survival according to median VD/VT. (A) Distal CTEPH patients and median VD/VT 0.45. (B) PAH patients and median VD/VT 0.35.

predominantly distal or proximal.<sup>10</sup> The difference in VD/VT seen in this study may be explained by the preponderance of non-uniform perfusion defects such as those demonstrated on V/Q scan in distal CTEPH<sup>4</sup> (with V/Q scan typically normal in PAH<sup>24</sup>), where more uniform distribution of small vessel disease may minimize the dead-space effect. This is also supported by evidence that abnormal ventilation and ventilatory inefficiency are present in subjects with chronic thromboembolic disease (CTED) without resting PH.<sup>25,26</sup> Furthermore, the anatomic site of obstruction may also determine the degree of dead-space ventilation and V/Q mismatch. One study using the canine embolic model of PH identified greater V/Q mismatch in proportion to the diameter of bead embolization,<sup>27</sup> with very distal embolization (akin to PAH) causing minimal disruption of V/Q matching.

In our cohort, we found greater impairment of gas exchange in distal CTEPH than in PAH, with lower PaO<sub>2</sub> and higher (A-a)O<sub>2</sub> at rest and peak exercise. The differences in gas exchange between distal CTEPH and PAH could be explained by more pronounced blood flow redistribution in CTEPH due to non-uniform vascular obstruction,<sup>28</sup> resulting in the generation of lung units with low V/Q ratios.<sup>22,29</sup> Although cardiac output was not significantly different between the CTEPH and PAH groups at rest, exercise hemodynamics were not evaluated and the influence of exercise hemodynamics on exercise gas exchange was not determined.

We found a small but significant reduction in exercise capacity in the distal CTEPH group compared with the PAH group. Moreover, in our study, VO<sub>2</sub> was independently related to VD/VT in the distal CTEPH group but not in the PAH group. This supports the notion that different mechanisms influence exercise limitation and symptoms in distal CTEPH and PAH, with increased VD/VT contributing to exercise impairment in distal CTEPH. The important contribution of VD/VT to exercise capacity in distal CTEPH is supported by recent findings showing that, after balloon pulmonary angioplasty, distal CTEPH patients still display exercise limitation, elevated VE/VCO<sub>2</sub> and increased (A-a)O<sub>2</sub> despite hemodynamic normalization (i.e., mPAP < 25 mm Hg).<sup>30</sup> The clinical relevance of VD/VT in distal CTEPH was also illustrated by the association between VD/VT and NYHA FC, a major prognostic marker in PH. However, our results are in contrast to those of Zhai et al, who did not document a relationship between VD/VT and NYHA FC in CTEPH.<sup>10</sup> An explanation for the discordant findings is not readily apparent but may be due to possible differences in the presence of comorbid conditions that impact exercise capacity and FC status. Our study included a population of subjects free of other cardiorespiratory and/or musculoskeletal abnormalities that could impact exercise capacity. In another study, van der Plas et al found that, in CTEPH, VD/VT was associated with severity of dyspnea, as assessed by the Borg scale, with a significant improvement after PEA in both dyspnea and VD/VT, thus supporting our

findings.<sup>31</sup> Moreover, it is of interest that, despite both groups demonstrating similar resting hemodynamics and 6-minute walk distance, there was a difference in terms of NYHA classification. Because NYHA class is a reflection of a patient's exercise intolerance, it is possible that higher ventilatory demand (due to more dead space) explains the worse functional status in CTEPH patients.

Several studies have explored the variables associated with survival in non-operable CTEPH.<sup>32–34</sup> A recent prospective registry study showed that, in non-operable patients, the most important predictors of death were NYHA FC, right atrial pressure and comorbidities.<sup>32</sup> However, a long-term study of non-operable CTEPH patients treated with riociguat showed contrasting results, with no association between FC and survival but a positive correlation between 6-minute walk distance and N-terminal pro-B-type natriuretic peptide.<sup>33</sup> Another study, in which CPET was performed, showed that peak  $\text{VO}_2$  was of prognostic value in non-operable patients.<sup>34</sup> In our study, we found that VD/VT could distinguish patients with a higher risk of death in the distal CTEPH group but not in the PAH group, although a non-significant trend was observed in PAH patients. The reasons why survival is associated with VD/VT in distal CTEPH are not entirely understood. The larger dead space could be associated with poor response to medical therapy or may be correlated with the severity of vascular occlusion, which in turn determines the ability of the right heart to adapt to the increased after-load. The significant correlation between pulmonary vascular resistance and VD/VT in distal CTEPH but not in PAH (data not shown) lend support to this hypothesis. Although no statistically significant association was found between VD/VT and survival in the PAH group, there was a trend toward worse survival in those with higher VD/VT. Thus, we cannot exclude the possibility that the lack of an association between VD/VT and survival in PAH was due to insufficient power of our sample size.

## Limitations

This study was a single-center, retrospective investigation. We acknowledge that the distinction between non-operable distal CTEPH and operable proximal CTEPH is subjective and dependent on the surgical experience of the CTEPH team. However, this distinction is clinically relevant as it dictates management and all patients were considered to have distal non-operable disease based on multidisciplinary assessment at an experienced PH center. We also acknowledge that our survival results were derived from a univariate model, and thus further studies with larger samples will be needed to clarify the role of VD/VT in CTEPH survival. Exercise pulmonary hemodynamics tests were not performed and it is plausible that differences in exercise cardiac output, for example, could have influenced exercise capacity in our study patients. We cannot exclude that medical treatment may have played a role in modulating ventilatory efficiency during exercise.<sup>35</sup> Indeed, a recent study by Charalampopoulos et al showed that PAH therapy in

non-operable CTEPH patients was associated with a trend toward improvement in  $\text{VE}/\text{VCO}_2$  and higher peak exercise  $\text{PaCO}_2$ , suggesting reduced hyperventilation after drug therapy.<sup>36</sup> Although the distal CTEPH patients received less specific therapy compared with their PAH counterpart, it is unlikely that drug therapy was the sole reason for the observed differences in CPET profiles between the 2 groups.

In conclusion, we have demonstrated greater exercise impairment, worse ventilatory efficiency and more abnormal gas exchange in distal CTEPH compared with PAH. Greater dead-space ventilation was associated with worse survival in the distal CTEPH patients. Our results suggest that VD/VT could be a major clinical marker of disease severity and prognosis in distal CTEPH.

## Disclosure statement

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## Appendix A. Supplementary material

Supplementary materials associated with this article can be found in the online version at [www.jhltonline.org/](http://www.jhltonline.org/).

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