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Cardiopulmonary Exercise Testing in Combined Pulmonary Fibrosis and Emphysema

Michael Westhoff[a, b] Patric Litterst[a] Ralf Ewert[c]

[a]Department of Pneumology, Sleep and Respiratory Medicine, Hemer Lung Clinic, Hemer, Germany; [b]University Witten/Herdecke, Witten, Germany; [c]Department of Internal Medicine, University Medicine, Greifswald, Germany

Keywords
Cardiopulmonary exercise testing · Combined pulmonary fibrosis and emphysema · Pulmonary hypertension

Abstract
Background: Combined pulmonary fibrosis and emphysema (CPFE) is a distinct entity among fibrosing lung diseases with a high risk for lung cancer and pulmonary hypertension (PH). Notably, concomitant PH was identified as a negative prognostic indicator that could help with early diagnosis to provide important information regarding prognosis. ***Objectives:*** The current study aimed to determine whether cardiopulmonary exercise testing (CPET) can be helpful in differentiating patients having CPFE with and without PH. ***Methods:*** Patients diagnosed with CPFE in 2 German cities (Hemer and Greifswald) over a period of 10 years were included herein. CPET parameters, such as peak oxygen uptake (peak VO_2), functional dead space ventilation (V_{Df}/V_T), alveolar-arterial oxygen difference ($AaDO_2$), arterial-end-tidal CO_2 difference [$P(a\text{-}ET)CO_2$] at peak exercise, and the minute ventilation-carbon dioxide production relationship (VE/VCO_2 slope), were compared between patients with and without PH. ***Results:*** A total of 41 patients with CPET (22 with PH, 19 without PH) were analyzed. Right heart catheterization was performed in 15 of 41 patients without clinically relevant complications. Significant differences in peak VO_2 (861 ± 190 vs. 1,397 ± 439 mL), VO_2/kg body weight/min (10.8 ± 2.6 vs. 17.4 ± 5.2 mL), peak $AaDO_2$ (72.3 ± 7.3 vs. 46.3 ± 14.2 mm Hg), VE/VCO_2 slope (70.1 ± 31.5 vs. 39.6 ± 9.6), and peak $P(a\text{-}ET)tCO_2$ (13.9 ± 3.5 vs. 8.1 ± 3.6 mm Hg) were observed between patients with and without PH ($p < 0.001$). Patients with PH had significantly higher V_{Df}/V_T at rest, V_{T1}, and at peak exercise (65.6 ± 16.8% vs. 47.2 ± 11.6%; $p < 0.001$) than those without PH. A cutoff value of 44 for VE/VCO_2 slope had a sensitivity and specificity of 94.7 and 72.7%, while a cutoff value of 11 mm Hg for $P(a\text{-}ET)CO_2$ in combination with peak $AaDO_2$ >60 mm Hg had a specificity and sensitivity of 95.5 and 84.2%, respectively. Combining peak $AaDO_2$ >60 mm Hg with peak VO_2/body weight/min <16.5 mL/kg/min provided a sensitivity and specificity of 100 and 95.5%, respectively. ***Conclusion:*** This study provided initial data on CPET among patients having CPFE with and without PH. CPET can help noninvasively detect PH and identify patients at risk. $AaDO_2$ at peak exercise, VE/VCO_2 slope, peak $P(a\text{-}ET)CO_2$, and peak VO_2 were parameters that had high sensitivity and, when combined, high specificity.

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Michael Westhoff
Department of Pneumology
Sleep Medicine and Intensive Care, Hemer Lung Clinic
Theo-Funccius-Str. 1, DE–58675 Hemer (Germany)
michaelwesthoff.mail@t-online.de

Background

Combined pulmonary fibrosis and emphysema (CPFE), first described in 1974 [1], is characterized by emphysema particularly in the upper lobes and fibrosis in the lower lobes [2–6]. Over the last several years, this condition has gained increasing attention considering that it represents a particular entity among interstitial lung diseases.

Studies have shown that patients with CPFE are at high risk for lung cancer and pulmonary hypertension (PH) [6–8] and have survival rates similar to those with idiopathic pulmonary fibrosis (IPF) [9, 10]. PH has been found to increase the risk of early mortality, with rates even comparable to idiopathic PH [13]. Therefore, PH represents an independent negative predictor [11, 12], the detection of which is crucial for risk assessment.

Patients, mainly smokers, complain about dyspnea and mostly have normal static and dynamic lung volumes but moderately to severely reduced diffusion capacity [7]. This suggests that using normal spirometry as the first diagnostic tool may not accurately determine the degree of dyspnea and severity of gas exchange impairment and thus may not be helpful in the early detection of CPFE, especially concomitant PH. This study, therefore, investigated whether cardiopulmonary exercise testing (CPET) can be helpful in differentiating patients with CPFE according to the presence or absence of PH.

Methods

Patients

Patients diagnosed with CPFE in 2 German cities (Hemer and Greifswald) from January 1, 2010, to December 31, 2019, were included herein. CPFE was diagnosed through typical computed tomography (CT) patterns indicating apical lung emphysema and basal fibrosis and typical lung function testing showing normal to slightly reduced inspiratory vital capacity (VC), forced expiratory VC (FVC), forced expired volume in 1 s (FEV_1), and diffusion capacity (TLCO). Only patients with CPET were included in this analysis. This study was approved by the Ethics Committee of Greifswald University (No. BB 057/2017). Consent to participation was provided verbally and partially through written consent.

Pulmonary Function Testing

Spirometry and body plethysmography were performed according to recommendations of the European Respiratory Society and American Thoracic Society [14].

Echocardiography

Patients underwent complete resting transthoracic echocardiography, which included 2-dimensional, pulsed, and continuous-wave Doppler and color flow imaging, conducted by an experienced investigator. Systolic pulmonary artery pressure (sPAP) was calculated from the maximum velocity of the tricuspid regurgitant jet using the Bernoulli equation, after which the estimated right atrial pressure based on inferior vena cava size and change in vessel caliber with respiration was added to this value [15]. PH was defined as sPAP >35 mm Hg at rest [16].

Right Heart Catheterization

Hemodynamic assessment in patients with clinical indications (pulmonary pressures not measurable or borderline at echocardiography, dyspnea inconsistent with normal or slightly increased pulmonary pressures in echocardiography, and exclusion of relevant postcapillary PH) was performed at rest using a standardized procedure in the supine position according to current guidelines [17–20]. PH was defined as mean PAP ≥25 mm Hg at rest [16].

Cardiopulmonary Exercise Testing

All patients performed an incremental CPET on a seated cycle ergometer, during which heart rate, pulse oximetry, and a 12-lead electrocardiogram were continuously recorded. Systolic and diastolic blood pressures were measured every 2 min. The exercise protocol included 3 min of rest and 3 min of unloaded paddling. The incremental increase was 10 or 15 Watt/min (Hemer) and 16 Watt/min (Greifswald). Exercise was stopped when subjects reached their symptom-limited maximum [21]. Gas exchange (VO_2, end-tidal CO_2 pressure [$PetCO_2$], end-tidal O_2 pressure [$PetO_2$], CO_2 production [VCO_2]) and ventilation (minute ventilation [VE], tidal volume [V_T], and respiratory rate [RR]) were assessed using breath-by-breath analysis. The functional dead space/tidal volume ratio (V_{Df}/VT) was calculated [22] by subtracting apparatus dead space from calculated VD according to the Enghoff modification of the Bohr equation and dividing it by VT: $V_{Df}/V_T = [(PaCO_2 - PECO_2) - (PaCO_2)] - [VD_m/V_T] \times 100$ (%), with VD_m representing the system dead space (mask, mouthpiece, etc.). Graphical presentations (Wasserman 9-panel plot) were generated computer-averaged over 10-s intervals. Peak VO_2 was defined as the highest oxygen uptake before the end of the exercise. The maximum voluntary ventilation (MVV) was calculated using a factor of 40 ($MVV40 = FEV_1 \times 40$) [23]. To calculate V_{Df}/V_T, $AaDO_2$, and $P(a\text{-}ET)CO_2$, capillary blood gases from hyperemized earlobes were obtained at rest, at peak exercise (every 2 min, at peak exercise, and after recovery), and V_{T1} (defined following the recommendations of the German working group on CPET and approximately corresponds to the anaerobic threshold) [24].

Statistical Analysis

Statistical analyses were conducted using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA). Data are presented as means and standard deviation, with a p value of <0.05 indicating statistical significance during 2-sided t tests. The relationship between variables was analysed by using Pearson's correlation coefficient.

Results

Patients

A total of 24 (males, $n = 20$; females, $n = 4$; age 67.4 ± 9.5 years; BMI 26.8 ± 4.6 kg/m^2) and 17 (males, $n = 16$;

Table 1. Demographic parameters of patients having CPFE with and without PH

	All, $n = 41$	PH, $n = 22$	No PH, $n = 19$	p value (PH vs. no PH)
Gender (male/female)	36/5	20/1	15/4	
Age, years	69.4±9.2	73.3±8.2	66.1±8.8	0.009
Weight, kg	80.3±13.7	81.4±11.3	79.3±15.6	ns
Height, cm	172.3±8.0	172.0±7.4	172.6±8.6	ns
BMI, kg/m^2	27.0±4.1	27.6±3.8	26.5±4.3	ns

CPFE, combined pulmonary fibrosis and emphysema; PH, pulmonary hypertension; ns, non-significant.

Table 2. Functional parameters of patients having CPFE with and without PH

	All, $n = 41$	PH, $n = 22$	No PH, $n = 19$	p value (PH vs. no PH)
FEV 1, %-pred.	93.8±17.7	88.0±19.7	98.8±14.3	0.049
VC, %-pred.	95.4±17.6	87.5±20.5	102.3±11.1	0.006
TLC, %-pred.	94.1±16.1	87.4±12.6	99.7±16.8	0.014
RV/TLC, %-pred.	93.8±19.9	96.8±18.0	91.2±21.6	ns
pO_2, mm Hg	65.1±12.8	56.6±10.1	71.6±10.7	<0.0001
pCO_2, mm Hg	34.8±3.6	33.9±3.2	35.6±3.7	ns
SaO_2, %	92.6±4.9	89.5±5.8	95.0±2.0	0.01

CPFE, combined pulmonary fibrosis and emphysema; PH, pulmonary hypertension; ns, non-significant<clear-delete>.</clear-delete>

Table 3. Cardiopulmonary exercise testing parameters in patients having CPFE with and without PH

	All, $n = 41$	PH, $n = 21$	No PH, $n = 19$	p value (PH vs. no PH)
Load, %-pred.	72.3±26.3	64.5±22	79.1±28.5	ns
Peak VO_2, mL	1,139±431	861±190	1,379±439	0.001
Peak VO_2, %-pred.	63.6±22.1	50.8±16.2	74.6±20.6	0.001
VO_2/kg/min, mL/kg/min	14.3±5.3	10.8±2.58	17.4±5.2	0.0001
VO_2/kg/min, %-pred.	63.07±21.9	49.6±14.8	74.7±20.6	0.0001

CPFE, combined pulmonary fibrosis and emphysema; PH, pulmonary hypertension; ns, non-significant.

females, $n = 1$; age 72.6 ± 8.2 years; BMI 27.3 ± 3.4 kg/m^2) patients with CPFE were identified from Hemer and Greifswald, respectively. No significant differences in age and BMI were observed between patients from both sites (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000513848).

Echocardiography

All patients underwent complete resting transthoracic echocardiography. No systolic left ventricular dysfunction or relevant valve defects were documented. After calculating sPAP in all patients, 19 were found to have PH.

Right Heart Catheterization

Right heart catheterization in 15 of 41 patients without clinically relevant complications confirmed either echocardiographically estimated pressures or echocardiographical suspicion of normal or elevated pulmonary artery pressure in 12 patients.

Lung Function Testing and Blood Gas Analysis

Patients with PH (following echocardiography and/or right heart catheterization) were significantly older (Table 1) and had significantly lower PO_2 and SaO_2, as well as %-predicted (%-pred.) values of FEV_1, VC, and TLC (Table 2), compared to those without PH. Significant dif-

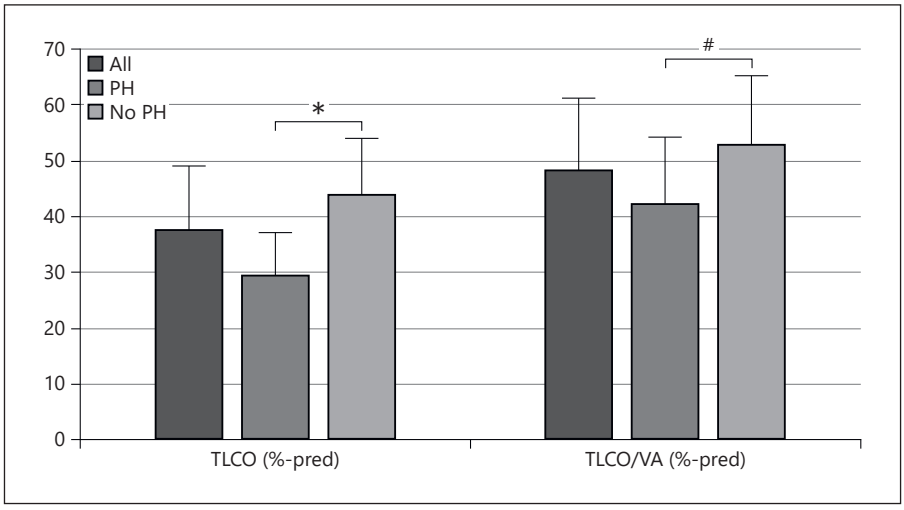

Fig. 1. TLCO and TLCO/VA (%-pred. values) in all patients having combined pulmonary fibrosis emphysema with and without PH (*$p < 0.0001$ and #$p < 0.01$). PH, pulmonary hypertension; TLCO, transfer factor of the lung for carbon monoxide; TLCO/VA, TLCO per alveolar volume.

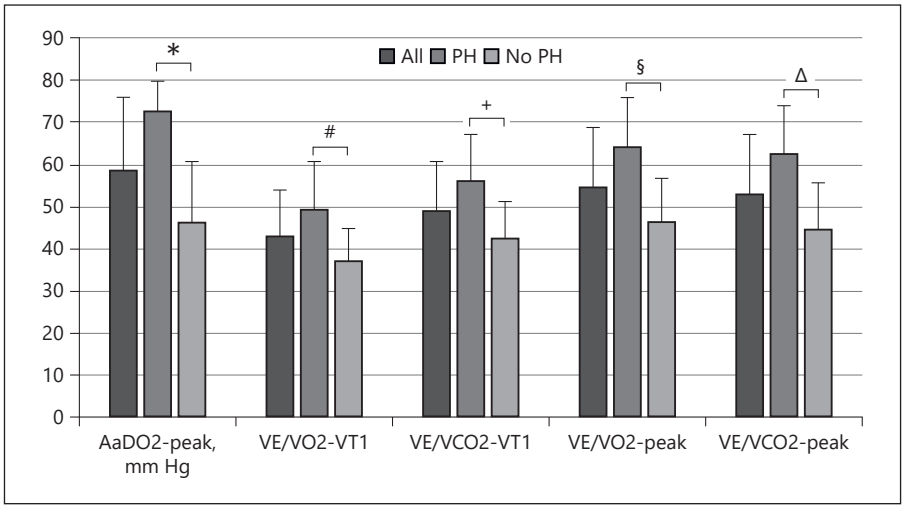

Fig. 2. Peak alveolar-arterial oxygen difference ($AaDO_2$) (*$p < 0.00001$), ratio of ventilation to carbon dioxide output (VE/VO_2), and VE/VCO_2 at V_{T1} (#/+ $p < 0.001$ each) and peak exercise (§/Δ $p < 0.0001$ each) in all patients having combined pulmonary fibrosis emphysema with and without PH. PH, pulmonary hypertension.

ferences in TLCO and TLCO related to alveolar volume (TLCO/VA) (%-pred.) ($p < 0.0001$) were observed between both groups (Fig. 1).

All patients with CPFE had the following values: FEV_1, 2.66 ± 0.65 L (93.46 ± 17.4%-pred.); VC, 3.62 ± 0.9 L (94.8 ± 17.3%-pred.); FEV_1%VC, 74.5 ± 10.9% (99.8 ± 14.4%-pred.); TLCO, 33.08 ± 1.15 mmol/L/min (33.64 ± 11.6%-pred.); TLCO/VA, 0.60 ± 0.16 (46.9 ± 13.1%-pred.); PO_2, 64.2 ± 12.7 mm Hg; PCO_2, 34.7 ± 3.7 mm Hg; and SaO_2, 92.5 ± 4.8 mm Hg. No significant differences were observed between patients from Hemer and Greifswald, except for PO_2, PCO_2, and SaO_2 (online suppl. Table 2).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise data (Table 3) showed a significant difference in peak VO_2 (peak oxygen consumption) between patients having CPFE with and without PH. Patients with PH had higher peak $AaDO_2$ and VE/VO_2- and VE/VCO_2-equivalents (ventilation equivalents for O_2 and CO_2) at V_{T1} and peak exercise (Fig. 2) and a significantly steeper VE/VCO_2 slope (Fig. 3) compared to those without PH. Additionally, patients with PH had a significantly greater V_{Df}/V_T at rest, V_{T1}, and at peak exercise than those without PH (Fig. 3).

$PetCO_2$ at peak exercise was lowest in patients with PH. Accordingly, those with PH had a higher P(a-ET)CO_2 at peak exercise but lower VO_2/Watt slope than those without PH (Fig. 4). Our results found positive correlations between VE/CO_2 slope and VD/V_T at V_{T1} ($r = 0.69$), peak $AaDO_2$ and peak P(a-ET)CO_2 ($r = 0.69$), and peak VD/V_T and peak $PetCO_2$ ($r = 0.61$).

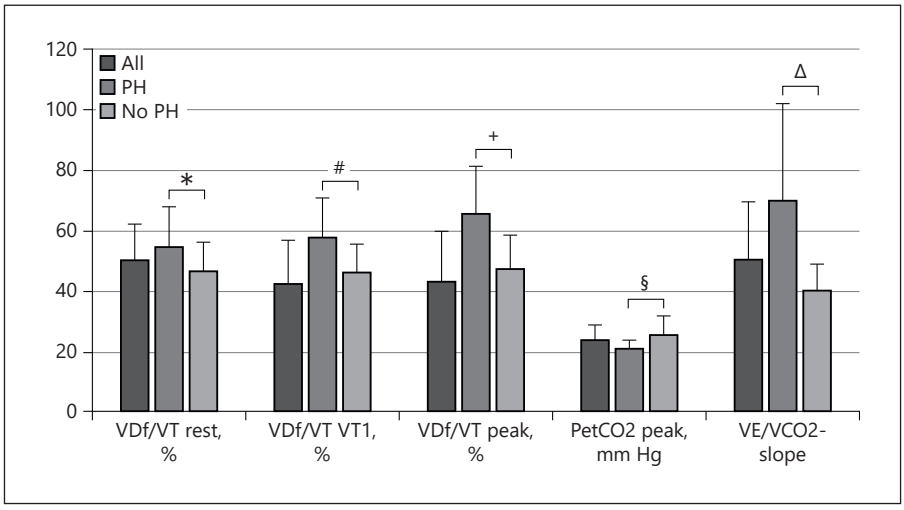

Fig. 3. Functional dead space ventilation (V_{Df}/V_T) (%) at rest (*$p < 0.05$), V_{T1} ($^{\#}p < 0.01$), and peak exercise ($^{+}p < 0.001$), end-tidal pressure of carbon dioxide ($PetCO_2$) at peak exercise (mm Hg) ($^{\S}p < 0.01$), and ratio of ventilation to carbon dioxide output (VE/VCO_2) slope at V_{T1} ($^{\Delta}p < 0.001$) in all patients having combined pulmonary fibrosis emphysema with and without PH. PH, pulmonary hypertension.

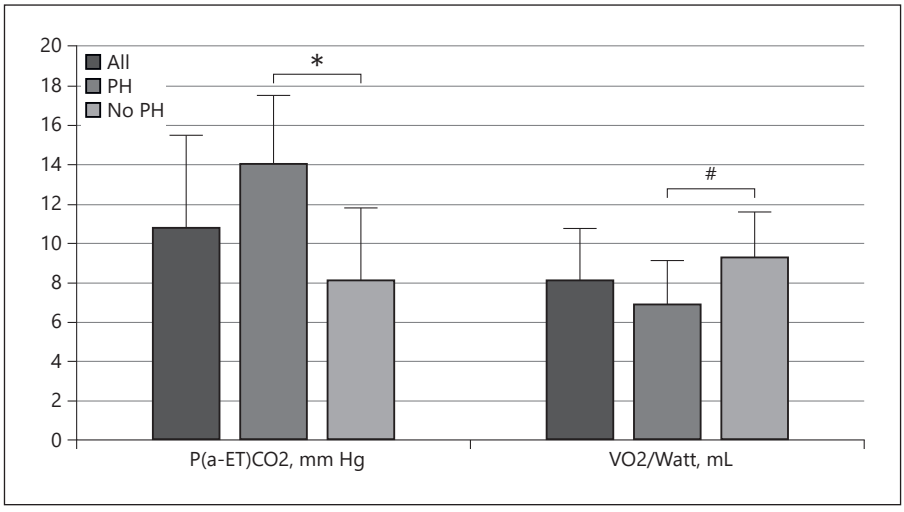

Fig. 4. Arterial to end-tidal carbon dioxide gradient [$P(a\text{-}ET)CO_2$] at peak exercise (mm Hg), and VO_2/Watt (mL/Watt) in all patients having combined pulmonary fibrosis emphysema with and without PH (*$p < 0.00001$ and $^{\#}p < 0.01$). PH, pulmonary hypertension.

Patients with normal pulmonary artery pressures only estimated by echocardiography exhibited significantly different CPET-parameters compared to those with elevated pulmonary artery pressures, either estimated only by echocardiography or determined by additional right heart catheterization. No significant differences in CPET parameters were observed between patients who had elevated pulmonary artery pressures estimated only via echocardiography and those who had additional evidence of PH via right heart catheterization (Table 4).

Noninvasive Prediction of Pulmonary Hypertension

A cutoff TLCO value of 33%-pred. produced a sensitivity and specificity of 76.5 and 88.9% for detecting PH, respectively. Moreover, peak $PetCO_2$ had a sensitivity and specificity of 78.9 and 94.7%, respectively, with a cutoff value of 11 mm Hg; however, using a cutoff value of 9 mm Hg increased sensitivity to 947% but decreased specificity to 63.6%. Peak $AaDO_2$ >60 mm Hg had a sensitivity and specificity of 100 and 72.7%, respectively.

Combining peak $AaDO_2$ >60 mm Hg and peak $P(a\text{-}ET)CO_2$ >9 mm Hg or VE/VCO_2 slope >44 produced a slight reduction in sensitivity to 90.9% but increased specificity to 94.7%. Using a cutoff value of 11 mm Hg for $PetCO_2$ in combination with a peak $AaDO_2$ >60 mm Hg provided a specificity and sensitivity of 95.5 and 84.2%, respectively. Maintaining a specificity of 95.5% further increased sensitivity to 100% when peak $AaDO_2$ >60 mm Hg was combined with peak VO_2/BW (body weight)/min <16.5 mL/kg/min.

Table 4. Cardiopulmonary exercise testing parameters in patients with CPFE: no pulmonary hypertension/only echocardiography versus PH/only echocardiography versus PH/echocardiography/right heart catheterization

	A: no PH/ only echo, $n = 19$	B: PH/ only echo, $n = 7$	C: PH/ echo/RHC, $n = 12$	p values A versus B* A versus C° B versus C#
Load, %-pred.	81.6±29.7	55.8±22.0	69.5±21.3	ns*,°,#
Peak VO_2, mL	1,419.1±446.0	824.0±240.0	881.8±161.3	0.001* 0.001° ns#
Peak VO_2, %-pred.	77.5±20.5	44.7±14.5	53.3±17.7	0.001* 0.002° ns#
VO_2/kg/min, mL/kg/min	17.9±5.3	10.6±2.9	10.8±2.9	0.003* 0.001° ns#
$AaDO_2$ peak, mm Hg	42.4±9.2	71.3±7.2	72.8±7.6	0.01* 0.0001° ns#
V_{Df}/V_T peak, %	44.8±7.2	74.4±15.8	60.4±13.9	0.008* 0.001° ns#
$P(a\text{-}ET)CO_2$ peak, mm Hg	7.7±3.7	14.7±3.1	13.5±3.8	0.01* 0.001° ns#
VE/VCO_2 slope at V_{T1}	37.2±7.5	82.9±49.4	62.7±11.2	0.01* 0.0001° ns#

CPFE, combined pulmonary fibrosis and emphysema; PH, pulmonary hypertension; ns, non-significant.

Discussion

To the best of our knowledge, this has been the first study to investigate whether CPET parameters among patients with CPFE could be helpful in characterizing those with PH. Our results showed that noninvasive parameters of gas exchange, such as $AaDO_2$, $PetCO_2$, and peak oxygen uptake, and ventilatory efficiency differed significantly between patients with and without PH. While $AaDO_2$ and $PetCO_2$ individually allowed the detection of PH with high sensitivity and specificity, their combination produced even higher sensitivities and specificities. Additionally, lung function parameters (FEV_1, VC, and especially TLCO at each %-pred.) and blood gas analysis data (PO_2 and/or SaO_2) can be helpful in the detection of PH in patients with CPFE.

Sun et al. [25] found that the pathological characteristics of ventilatory efficiency, oxygen uptake, and oxygen uptake related to work rate in patients having CPFE with PH at rest were similar to those observed in patients with idiopathic PH such that peak VO_2 and cardiac output were inversely correlated with mean PAP. Furthermore, they showed that an increase in $AaDO_2$, dead space ventilation, and VE/VCO_2 at the anaerobic threshold correlated with mean PAP, whereas a decrease in $PetCO_2$ due to exercise hyperventilation was inversely correlated with PH severity. All patients with PH included herein had $PetCO_2$ values below 30 mm Hg, with a mean $PetCO_2$ of 22.4 mm Hg, which have been reported to be correlated with at least moderate and severe PH [25].

To date, no study has compared CPET data according to the presence or absence of PH among patients with

CPFE. Given that fibrosis remains most relevant pathology determining prognosis in CPFE, IPF data appear to be useful for further comparison. Published data [26, 27] have shown that survival among patients with IPF is primarily influenced by the occurrence of PH. Indeed, one study showed that among 38 patients with IPF, 11 (29%) of whom had sPAP ≥40 mm Hg, a $VE/VCO_2 > 45$ at the anaerobic threshold allowed significant differentiation between those with and without PH (PH estimated with sPAP ≥40 mm Hg) [26]. Those with a $VE/VCO_2 > 45$ at the anaerobic threshold had a significant lower survival compared to those with a $VE/VCO_2 \leq 45$, whereas sPAP did not allow survival prediction. This corresponded with the VE/VCO_2 at V_{T1} and VE/CO_2 slopes of our patients with CPFE and PH. Another study [27] showed that peak VO_2 and VE/VCO_2 slope differed significantly ($p < 0.001$) between patients having IPF with and without PH (peak VO_2: 810.4 [579.6, 1,012.0] vs. 1,161.3 [870.1, 1,493.1] and VE/VCO_2 slope [48 vs. 32]) and allowed differentiation between both groups – a finding consistent with that presented herein.

Leveneziana et al. [28] found that 8 patients with pulmonary veno-occlusive disease had significantly lower $PetCO_2$ values, higher VE, and consequently higher VE/VCO_2 slopes compared to 16-matched patients with PAH. Interestingly, patients with CPFE and PH had nearly identical absolute values of $P(a\text{-}ET)CO_2$, $AaDO_2$, and V_{Df}/V_T compared to those with pulmonary veno-occlusive disease at comparable workloads [29]. Moreover, patients with CTEPH exhibited a significantly higher peak V_{Df}/V_T (0.64 ± 0.10%) compared to those with PAH (49 ± 0.08%) [30]. This, together with the positive correlations found between V_{Df}/V_T, $PetCO_2$, and VE/CO_2 slope, underline the additional relevance of dead space ventilation and its influence on gas exchange, especially increased VE/VCO_2, as previously described [31].

A recent study [32] that compared sensory and physiological responses to exercise between patients with CPFE and those with IPF showed that the former had significantly lower peak exercise capacity, lower breathing reserve, and higher VE/VCO_2 nadir, which were associated with a steeper VE/VCO_2 slope and worse exertional dyspnea. Although patients with greater dyspnea presented with lower transfer factor, lower $PaCO_2$, and higher resting VD/V_T ratio, no echocardiography variable was found to be associated with dyspnea burden, while no significant associations between echocardiographic indicators of PH and ventilatory inefficiency or VD/V_T were found among those with CPFE, which contradicts our results. However, patients included in the aforementioned study had ventilator impairment with TLCO values >30%, which did not fall within the range (20–30%) found to be associated with a higher likelihood of PH in the previous studies [9] and the present work. Our findings showed that patients with PH had significantly lower TLCO than those without PH, suggesting the negative influence of additional vascular pathology on TLCO in CPFE with PH. Therefore, severely impaired TLCO also needs to be considered a marker of a worse prognosis.

Survival of patients with CPFE is mainly determined by underlying interstitial fibrosis given that the presence and extent of emphysema were found to have no impact on survival [33]. Patients having CPFE with and without PH included herein had normal FEV_1 and VC. However, those with PH had significantly lower predicted values of the mentioned parameters. Despite the absence of additional CT evaluation, it can be argued that the reduction in FEV_1 and VC might be associated with the extent of fibrosis and might have an impact on the development of PH. Given that patients with PH were significantly older than those without PH, the difference in age needs to be considered a factor in the progression of fibrosis, resulting in the reduction of lung volumes and increased pulmonary artery pressures.

Most patients with CPFE present with dyspnea but typically have normal spirometry values, which increases the risk for delayed CPFE diagnosis given the difficulty of diagnosis without high-resolution CT. As such, basal velo crackles and normal spirometry during the examination of patients with exertional dyspnea should be a criterion for additional echocardiography and/or CPET to earlier identify those with CPFE, especially those with PH, given their poor prognosis. Therefore, a comprehensive evaluation of these patients, including their exercise limitation, is desirable. Accordingly, CPET represents a safe method for evaluating exercise limitations even for patients with severe PH and hypoxemia [33, 34]. As indicated by Balady et al. [35], hypoxemia itself is not an indication to discontinue exercise tests but instead requires integration with clinical judgment [35].

Studies have shown that CPET parameters predict survival in patients with PAH and offer additional information on the prognostic value of the 6-min walk test [36–38]. Furthermore, CPET may rouse suspicion of, and even confirm, underlying PH without additional right heart catheterization in patients with dyspnea and normal spirometry but low TLCO considering the significant differences in CPET parameters between those with normal pulmonary artery pressures determined through echocardiographic evaluation alone and those with ele-

vated pressures determined through either echocardiography alone or additional invasive measurements.

These advantages and synergism with echocardiography support the functional evaluation of patients with suspected or confirmed PAH using CPET, especially when echocardiography is inconclusive [39, 40]. However, this approach would necessitate regular obtaining blood samples during CPET.

The current study has some limitations worth noting. First, not all patients underwent right heart catheterization. Second, given that patients had not been followed up, we could not determine whether those surpassing the suggested abnormal threshold of VE/VCO_2 slope had worse prognosis. Third, 3 patients with normal pulmonary artery pressures at rest showed a left-shift and increase in the VE/VCO_2 slope during exercise, we could not exclude the possibility of exercise PH given that they did not undergo additional exercise testing with right heart catheterization. Nonetheless, further CPET, parameters (peak $AaDO_2$, peak V_{Df}/V_T, VE/VCO_2, at V_{T1}) of these few patients were similar to those of patients with PH and significantly differed from those with patients without PH.

Conclusion

The present study has been the first to provide data regarding CPET in patients having CPFE with and without PH, subsequently showing significant differences in CPET parameters between both groups. Notably, $AaDO_2$ at peak exercise, VE/VCO_2 slope, peak $PetCO_2$, and peak VO_2 were identified as parameters with high sensitivity and, when combined, high specificity for differentiating patients having CPFE with and without PH. As such, CPET can help noninvasively detect PH and identify patients at risk, especially when echocardiography is inconclusive.

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Statement of Ethics

This study was approved by the Ethics Committee of Greifswald University (No. BB 057/2017). Consent to participation was provided verbally and partially through written consent.

Conflict of Interest Statement

All the authors declare no relationships with any industry or competing conflicts of interest.

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No funding was received for this work.

Author Contributions

M.W., P.L., and R.E. contributed to data acquisition. M.W. and R.E. contributed to literature review, drafting, and revising the final draft. All the authors have read and approved this manuscript.

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