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RESEARCH LETTER

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Cardiopulmonary exercise testing and the 2022 definition of pulmonary hypertension

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Abstract

Parameters of cardiopulmonary exercise testing significantly discriminate between healthy subjects and patients with pulmonary hypertension (PH), also according to the new 2022 definition of pulmonary hypertension (mean pulmonary arterial pressure mPAP > 20 mmHg). The cut-offs indicating on PH were peakVO_2 ≤ 16.7 mL/min/kg (Youden-Index YI = 0.79), $p_{et}CO_2$@AT ≤ 34 mmHg (YI = 0.67), and VE/VCO_2@AT ≤ 30 (YI = 0.76).

KEYWORDS
cardiopulmonary exercise, peakVO_2, $p_{et}CO_2$@AT, pulmonary hypertension, VE/VCO_2@AT

Abbreviations: AT, anaerobic threshold; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; ESC, European Society of Cardiology; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; $p_{et}CO_2$@AT, end-tidal partial pressure of carbon dioxide at anaerobic threshold; $p_{et}CO_2$, end-tidal partial pressure of carbon dioxide; PAH, pulmonary arterial hypertension; peakVO_2, maximum oxygen uptake per minute at exercise; PH, pulmonary hypertension; RHC, right heart catheterization; ROC, receiver operating characteristic; SHIP, Study of Health in Pomerania; VE/VCO_2@AT, ventilation to carbon dioxide output ratio at anaerobic threshold; VE/VCO_2, ventilation to carbon dioxide output ratio; VE/VCO_2-slope, slope of the relation of ventilation and carbon dioxide output, ventilatory efficiency; VT1, ventilatory threshold 1; YI, Youden-Index.

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Pulmonary hypertension (PH) is an important differential diagnosis in patients with unexplained dyspnea. The diagnostic algorithm of the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH[1] recommends for these patients in Step 1 ("suspicion") medical history, physical examination, electrocardiogram, chest X-ray and laboratory values, and in Step 2 ("detection") both echocardiography and cardiopulmonary exercise testing (CPET) at an early stage of work-up. Both methods share the advantage of being noninvasive, in which the echocardiography is regarded as primary decisive method.[2] If echocardiography reveals PH as a possible cause of dyspnea, step 3 ("confirmation") will require right heart catheterization (RHC); and the 2022 guidelines define PH by a mean pulmonary artery pressure (mPAP) > 20 mmHg at rest.[1] The general correlation between echocardiographic estimated pulmonary pressure and invasively measured mPAP is good but the individual calculation from tricuspid regurgitation delivers correct values in only 50% of patients.[3,4] However, the aim of echocardiography as a screening tool lies in detection of patients with suspicion of PH and not in accurate assessment of mPAP. Insufficient quality of echocardiographic signals might be a further limitation of echocardiography, namely, in patients with chronic obstructive pulmonary disease (COPD).[3] Therefore, the 2022 guidelines recommend CPET as helpful to detect PH and to assess the underlying pathophysiological mechanisms. Patients with pulmonary arterial hypertension (PAH) show a typical pattern of low endtidal partial pressure of carbon dioxide ($p_{et}CO_2$), high ventilatory equivalent for carbon dioxide (VE/VCO_2), and low peak oxygen uptake ($peakVO_2$).[5,6] Lowering the threshold for PH and in this way moving pathology closer to normal could theoretically weaken the diagnostic tool of CPET. The purpose of our retrospective study was to investigate whether these CPET parameters still discriminate between healthy individuals and PH patients according to the new cut-off for mPAP > 20 mmHg. We included 3377 healthy subjects from the Study of Health in Pomerania (SHIP), and 753 patients from the PH outpatient department of the University Medicine Greifswald, Germany. In detail, these patients were recruited from 994 patients who had been referred to our outpatient department between 2002 and 2021 with the diagnosis "dyspnea." Moreover, 753 had a CPET at first visit, and the consecutive diagnostic work-up with RHC revealed that 164 of these patients had a mPAP <20 mmHg, so that the remaining 589 patients were included in this study. Due to missing data of $p_{et}CO_2$@AT and VE/VCO_2@AT another 65 patients had to be excluded. The final study sample comprised of 524 patients. Out of these 315 patients had a PAH and were analyzed as predefined subgroup. The SHIP studies analyzed a strictly healthy population resident in the very catchment area and recruited in the same decades. Intention and method of SHIP have been described elsewhere in detail.[7] The ventilatory threshold 1 was identified as the point of transition in the VCO_2 versus VO_2 slope from <1 to >1 ("V-slope method"). In cases where the V-slope method could not be applied, ventilatory threshold 1 (VT1) was defined as the lowest point of the ventilatory equivalent for oxygen (VE/VO_2). Please note that the old term "anaerobic threshold (AT)" is used in this article instead of the new standardized term "VT1" because this nomenclature corresponds with the cited studies. Data were given as median with interquartile range (IQR) in square brackets. Receiver operating characteristic (ROC) curves were conducted and the area under the curve (AUC) was calculated. The Youden index (defined as sensitivity + specificity − 1) was used to define best cut-off values of $p_{et}CO_2$@AT, VE/VCO_2@AT, and $peakVO_2$ that discriminate PH patients from healthy individuals. Differences between the numeric variables with nonparametric distribution were calculated by Mann–Whitney *U t* test, and for gender as a categorical variable by Pearson χ^2 test. Demographic data were different for age and body mass index (BMI) and comparable for sex. The healthy persons had a median age of 51.0 years ([IQR: 40.0; 62.0], range 20–85) and 51.3% were female. The patient group had a slightly lower proportion of females (48.9%; Pearson χ^2 vs. healthy = 0.300) but were older (68.9 years [59.4; 76.8], range 18–91 years; $p < 0.001$) and had a somewhat higher BMI (patients 28.3 kg/m^2 [24.4; 30.6] vs. healthy 27.3 kg/m^2 [24.4; 30.6]; $p < 0.001$). All CPET parameters were significantly different between patients and healthy individuals, with all $p < 0.001$:

$peakVO_2$: patients 12.2 mL/min/kg [9.9; 14.6] healthy 24.7 mL/min/kg [20.3;29.5]

$peakVO_2$%predicted: patients 55.6% [44.7; 68.0] healthy 96.2% [85.4; 108.4]

$p_{et}CO_2$@AT: patients 27.9 mmHg [23.2;33.0] healthy 39.8 mmHg [37.0; 43.0]

VE/VCO_2@AT: patients 40.9 [33.5; 49.8] healthy 26.0 [25.0; 29.0].

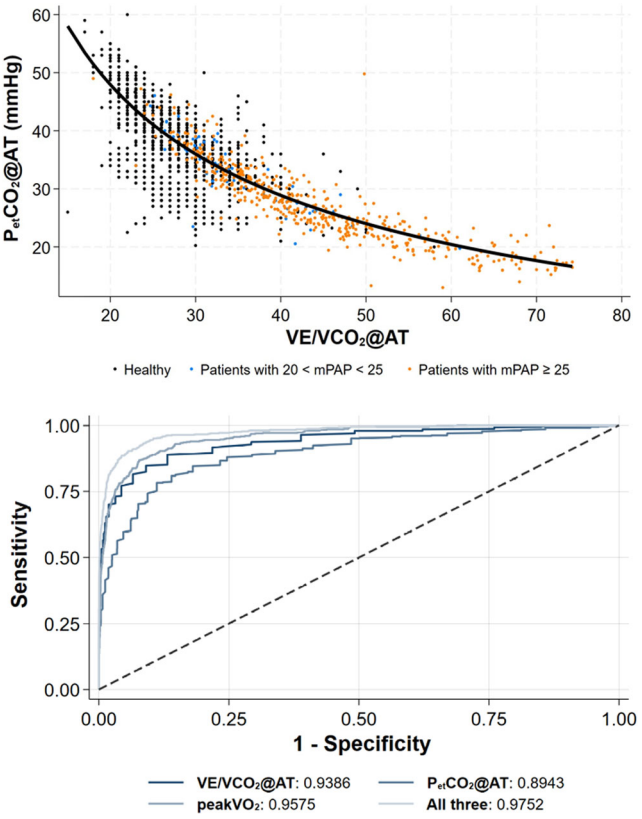

FIGURE 1 Above: $p_{et}CO_2$@AT versus VE/VCO_2@AT in healthy subjects (black), and in pulmonary hypertension patients according to the 2015 definition (orange) and additionally 2022 definition (blue). Below: Receiver operating characteristics of the three parameters with best discrimination between patients and healthy individuals. $p_{et}CO_2$@AT, end-tidal partial pressure of carbon dioxide at anaerobic threshold; peakVO_2, maximum oxygen uptake per minute; VE/VCO_2@AT, ventilation to carbon dioxide output ratio at anaerobic threshold.

We found a strong hyperbolic relation between $p_{et}CO_2$@AT and VE/VCO_2@AT both in patients and healthy individuals (Figure 1). The cut-offs indicating on PH were peak$VO_2 \leq 16.7$ mL/min/kg (Youden-Index YI = 0.79), $p_{et}CO_2$@AT ≤ 34 mmHg (YI = 0.67), and VE/VCO_2@AT ≥ 30 (YI = 0.76). The application of the revised criteria detected 179 patients more than the conventional definition, and the analysis of the patients covered by the old PH definition showed the cut-offs $p_{et}CO_2$@AT ≤ 30 mmHg (YI = 0.55), and VE/VCO_2@AT ≥ 40 (YI = 0.53). Using the new definition, the parameter with the best discrimination between patients and healthy individuals was peakVO_2 (AUC = 0.96), followed by VE/VCO_2@AT (AUC = 0.94) and $p_{et}CO_2$@AT (AUC = 0.89). The combination of these three parameters had a ROC of 0.98. Figure 1 displays the patients who were additionally detected with the new cut-offs in blue. The cut-offs for the subgroup of 315 patients with pulmonary arterial hypertension, defined by mPAP > 20 mmHg, pulmonary vascular resistance > 2 wood units and pulmonary wedge pressure ≤ 15 mmHg, were peak$VO_2 \leq 16.7$ mL/min/kg (YI = 0.80), $p_{et}CO_2$@AT ≤ 34 mmHg (YI = 0.75), and VE/VCO_2@AT ≥ 32 (YI = 0.82). The difference to healthy individuals was again significant with $p < 0.001$.

Our data show that CPET parameters allow an excellent discrimination between healthy subjects and patients with PH even after lowering the cut-off for mPAP according to the 2022 definition. The data of the 179 additionally diagnosed patients move the CPET parameters somewhat towards the normal, that is, to higher peakVO_2 and $p_{et}CO_2$@AT and lower VE/VCO_2@AT, but nevertheless these parameters separate PH from normal. This discrimination remained significant for the subgroup of patients with PAH.

Our study is the first to deliver large-scale data on healthy subjects that cover the area above 36 mmHg $p_{et}CO_2$@AT. This confirms the pathophysiological link between VE/VCO_2@AT and $p_{et}CO_2$@AT as described by Yasunobu et al.[5] The latter study was already conducted in 2005 and was based on a $p_{et}CO_2$@AT > 36 mmHg in nine healthy volunteers only. Our study fills this gap, proves the hyperbolic relation between $p_{et}CO_2$@AT and VE/VCO_2@AT and validates this relation in both healthy subjects and PH patients. A pathophysiological interpretation might be that a healthy lung/lung-perfusion system tolerates imbalances between ventilation and perfusion, whereas an increasing, pathological ventilation-perfusion mismatch uniquely forces to hyperventilation. Figure 1 visualizes these different pathophysiological items: At the pathological and PH representing end of the *x*-axis, the increase in arterial pCO_2 can only be covered by an increase in ventilatory work, but the factors contributing to PH like ventilation-perfusion-mismatch, impaired right ventricular function, impaired diffusion capacity, and muscle coupling to ventilation prevent an adequate exhalation of CO_2. As PH increases, the mismatch between ventilation and CO_2-production (as VE/VCO_2@AT) becomes greater, ventilatory work is "wasted" and thus the $p_{et}CO_2$@AT becomes lower. At the physiological end of the scale, p_aCO_2 is still the ventilatory drive, but ventilation and perfusion are exactly tuned. Individual differences in the CO_2 eliminating chain "muscle-blood-heart-lung" allow different relations between $p_{et}CO_2$ and VE/VCO_2, thus explaining that the variance is higher between normal subjects than between PH patients. Finally, this relation is a nonlinear one, because a linear link would implicate the existence of intercepts with both axes, and these zero points have no physiological explanation. They would require the existence of a lowest limit for $p_{et}CO_2$ (intercept with

the *x*-axis) and for VE/VCO_2 (intercept with the *y*-axis, corresponding to a breathing arrest with still emitted CO_2). A recent study on PAH patients found similarly such a strong hyperbolic relation for $p_{et}CO_2$ and VE/VCO_2-slope, but still used the old cut-off for mPAP, took $p_{et}CO_2$ at peak exercise (which might differ slightly from $p_{et}CO_2$@AT) and included only nine patients with a $p_{et}CO_2$@peak > 36 mmHg.[6] Another CPET study on heart failure patients found a strong correlation between VE/VCO_2@AT and $p_{et}CO_2$@AT but hypothesized a linear relationship.[8] Our cut-offs are in line with values by Held et al. who showed that among others VE/VCO_2-slope > 35 and $p_{et}CO_2$@AT < 35 mmHg were suggestive for disturbed pulmonary perfusion.[9] A recent study by the same working group showed that defining PH by 20 mmHg instead of ≥25 mmHg led to a relative increase of 23.5% of the diagnosis rate of CTEPH.[10] This is comparable to the increase of 30% in our study with PH patients of different aetiologies. One must consider that both echocardiography[4] and CPET should be an essential part of the diagnostic workup in PH at an early stage. In summary, our study shows that CPET parameters discriminate between healthy subjects and PH patients also according to the 2022 PH definition and a threefold combination of VE/VCO_2@AT, peakVO_2, and $p_{et}CO_2$@AT predicts PH with a high probability.

AUTHOR CONTRIBUTIONS

Dirk Habedank wrote the manuscript and contributed to the analysis. Till Ittermann and Anne Obst performed the statistical calculations and figures and contributed to the manuscript. Beate Stubbe, Alexander Heine, Sabine Kaczmarek, and Ralf Ewert performed the cardiopulmonary exercise testing, assessed the outpatients, and contributed to the manuscript. Ralf Ewert designed the study.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

All participants of the Study of Health in Pomerania (SHIP) and all patients from the pulmonary hypertension outpatient department of the University Medicine Greifswald gave their informed and written consent for the anonymous and condensed publication of the data. The study follows the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

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