The association of six-minute walk work and other clinical measures to cardiopulmonary exercise test parameters in pulmonary vascular disease

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Abstract

Introduction: In pulmonary vascular disease exercise, abnormalities can include reduced exercise capacity, reduced oxygen pulse and elevated VE/VCO_2. The association of clinical measures such as six-minute walk work, haemodynamics, lung function and echocardiogram to peak VO_2, O_2 pulse and VE/VCO_2 has not been fully investigated in pulmonary vascular disease.

Aims: To determine the relationship of six-minute walk work and other clinical measures to peak VO_2, peak O_2 pulse and VE/VCO_2. Additionally, to investigate the ability to predict peak VO_2 from six-minute walk work and other clinical parameters.

Methods: Clinical data was retrospectively analysed from 63 chronic thromboembolic pulmonary hypertension (CTEPH) and 54 chronic thromboembolic disease (CTED) patients. Six-minute walk test measures, haemodynamics, lung function and echocardiographic measures were correlated with peak VO_2, peak O_2 pulse and VE/VCO_2. Predictive equations were developed to predict peak VO_2 in both CTEPH and CTED cohorts and subsequently validated.

Results: A number of clinical parameters correlated to peak VO_2, peak O_2 pulse and VE/VCO_2. Six-minute walk work and transfer factor for carbon monoxide demonstrated the strongest correlation to peak VO_2 and peak O_2 pulse. The validation of the predictive equations showed a variable level of agreement between measured peak VO_2 and calculated peak VO_2 from the predictive equations.

Conclusion: Six-minute walk work and additionally a number of clinical test parameters were associated to peak VO_2, peak O_2 pulse and VE/VCO_2. Six-minute walk work and transfer factor for carbon monoxide were particularly highly correlated to peak VO_2 and similarly to peak oxygen pulse. The validation of the predictive equations showed a variable level of agreement and therefore may have limited clinical applicability.

Introduction

Exercise intolerance is a significant characteristic in patients with pulmonary vascular disease (PVD) and can be attributed to a variety of factors that include reduced cardiac output (CO) and under perfused alveoli caused by pulmonary vasculature remodelling.[1] Exercise capacity determination is of importance in pulmonary hypertension (PH) due to its association with survival and functional status.[2] The gold standard test for assessing exercise capacity is a cardiopulmonary exercise test (CPET). Clinical abnormalities from the CPET include reduced oxygen pulse (O_2 pulse) due

to a hindered ability to increase stroke volume (SV). PVD also displays signs of gas exchange and dead space problems which are identified through multiple parameters. One such parameter is the elevated ventilation (VE) to carbon dioxide production slope (VE/VCO_2 slope) which is elevated, throughout exercise, as a consequence of reduced perfusion

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of well-ventilated alveoli.[3] CPET in PH can be useful in determining disease severity and assess treatment effectiveness[3] and parameters such as peak oxygen consumption (VO_2) and VE/VCO_2 are of strong prognostic importance.[4] However, CPET is an expensive complex test requiring expertise and therefore not performed routinely. The ability to predict the outcomes of a CPET test from less complex and costly procedures would clearly be an advantage.

The six-minute walk test (6MWT) is often used as a surrogate for CPET, due to its simplicity. It is the most routinely performed exercise test in PVD to assess exercise capacity, is a predictor of survival and a widely used end point in clinical trials in PH. The 6MWT has limitations such as decreased sensitivity in detecting meaningful clinical change in patients with a better functional status especially in those who walk longer than 450 m[5]; this is known as the "ceiling effect". Additionally, six-minute walk distance (6MWD) is impacted by many factors such as gender, age, height comorbidities, motivation and learning effect and significant factors such as patient effort and stride length could be more impacting than exercise capacity on achieved 6MWD.[2,6] Furthermore, the 6MWD has demonstrated a poor predictive ability in predicting peak VO_2 (mL/min) in pulmonary arterial hypertension (PAH).[7] Importantly, the 6MWT does not account for the body habitus of the patient when walking, which will likely impact the acquired functional capacity. A measure which accounts for body habitus is six-minute walk work (6MWW), which is the product of 6MWD and body weight. A number of investigations have demonstrated a more superior relationship of VO_2 and 6MWW compared with 6MWD in PAH patients.[1,6,8] A recent review by the ERS/ATS Taskforce[9] on field exercise tests stated that additional studies are needed to better characterise the utility of 6MWW in adults with chronic respiratory disease. The utility of 6MWW in PVD is yet to be determined, such as whether it is able to accurately predict peak VO_2 across all PVD cohorts including chronic thromboembolic pulmonary hypertension (CTEPH) and chronic thromboembolic disease (CTED), a cohort that can exhibit exercise intolerance despite not presenting with PH at rest.

Haemodynamics are of prognostic significance in PVD, as they can be highly reflective of disease severity, and currently there has been limited investigation on how haemodynamics associate to CPET parameters.[10–13] Additionally, other clinical parameters measured from other clinical investigations include echocardiography, pulmonary function tests; there is also limited knowledge of how they may also associate to CPET parameters.

The objectives of this study, therefore, are to determine the relationship of 6MWW and/or other clinical parameters to peak VO_2 for CTEPH and CTED groups, the association to peak O_2 pulse, and VE/VCO_2 slope and to investigate the ability to predict peak VO_2 from 6MWW and other clinical parameters.

Method

This was a retrospective review analysis performed at Royal Papworth Hospital Cambridge, UK which was approved by the research and development department. Data was collected between 2015 and 2020 on 117 patients who performed a CPET, in which 37 of these patients had performed serial CPETs over this time period.

Subjects

The PVD population included 63 patients with CTEPH and 54 patients with CTED. Summaries of the PVD cohort characteristics are presented in Supplement Table 1.

The inclusion criteria for the study were: patients who performed a CPET and who had any of the following clinical investigations, 6MWT, pulmonary function tests, RHC or echocardiogram performed within a 60-day timeframe of their CPET and had not undergone any changes in their treatment.

CPET

CPET was performed using a cycle ergometer and metabolic system (Oxycon Pro, Vyaire UK Ltd). CPET was performed using a ramp protocol. CPETs were conducted by experienced physiologists and reviewed by two independent reporters. The work rate was individualised for each patient based on their age and weight. Adjustments to the predicted work rate were made based on the patient's self-described current exercise capacity. Patients were instructed to cycle at a cadence of 60–63 r/min throughout the test protocol until symptom limitation. During the test, VO_2, VCO_2 and VE were measured continuously using breath-by-breath analysis. VE/VCO_2 slope was calculated as the slope of VE versus VCO_2 prior to any respiratory compensation point, evident as an inflection point in this charted relationship. Heart rate (HR) and electrocardiogram (ECG) were measured by 12 lead ECG. All tests were symptom limited and terminated by the patient. Predicted peak VO_2 was calculated using Study of Health in Pomerania (SHIP)[14] predictive equation for patients aged over 21 and for patients aged below 21 Bongers predictive equation.[15] Sub-maximal tests were excluded from data analysis. A maximal test was defined as one or more of, heart rate reserve less than 16 beats per minute and/or ventilatory reserve of less than 15 L per minute.

6MWT

The 6MWT was performed on a 10-m corridor (2015–2019) and, due to hospital relocation from May 2019, was performed on a 30-m walk corridor. All Patients were given the same instructions by CD-player and were instructed to walk as far as possible in 6 min, but they could stop and rest when required and resume walking again when possible. The 6MWT was conducted under supervision by the

Table 1. Correlation coefficients of clinical parameters to peak VO2 (mL/min).

	CTEPH	CTED
Six-minute walk test		
6MWW (kg.m)	**0.83*** (n = 68)**	**0.77*** (n = 67)**
6MWD (m)	**0.62*** (n = 68)**	**0.62*** (n = 69)**
Haemodynamic parameters		
Systolic pulmonary pressure (mmHg)	**−0.73*** (n = 31)**	0.14 (n = 23)
mPAP (mmHg)	**−0.49*** (n = 63)**	0.26 (n = 34)
PCWP (mmHg)	**0.39** (n = 59)**	0.03 (n = 33)
CO [TD] (L/min)	**0.49*** (n = 62)**	**0.54*** (n = 34)**
CI [TD] (L/min^2)	0.14 (n = 43)	**0.62*** (n = 29)**
PVR [TD] (dyn.s.cm^{-5})	**−0.73*** (n = 54)**	−0.25 (n = 28)
CO [Fick] (L/min)	**0.52*** (n = 42)**	**0.78*** (n = 35)**
TPG (mmHg)	**−0.63*** (n = 50)**	0.25 (n = 20)
Pulmonary function parameters		
FEV1 (L)	**0.60*** (n = 31)**	**0.64*** (n = 68)**
VC max (L)	**0.55** (n = 31)**	**0.77*** (n = 68)**
TLCO (mmol/min/KPa)	**0.80*** (n = 31)**	**0.83*** (n = 68)**
KCO (mmol/min/KPa/L)	0.09 (n = 31)	**0.29* (n = 66)**
TLC (L)	**0.55** (n = 26)**	**0.74*** (n = 53)**
IC (L)	**0.68*** (n = 25)**	**0.77*** (n = 53)**
Echocardiogram parameters		
LVIDd (cm)	**0.61*** (n = 64)**	**0.58*** (n = 65)**
LVIDs (cm)	**0.44*** (n = 61)**	**0.46*** (n = 63)**
LV mass (g)	**0.56** (n = 64)**	0.52 (n = 61)
SV (LVOT) (mL)	**0.27* (n = 61)**	**0.46** (n = 58)**
TAPSE (cm)	0.16 (n = 62)	**0.36** (n = 60)**
RA area (cm^2)	−0.21 (n = 48)	**0.64***(n = 50)**

Note: Significant correlation coefficient (r) are highlighted in bold and significance level presented with ***p < 0.001; **p < 0.01; *p < 0.05). Note that EDP, RA pressure, CI Fick, SV index and RV basal diameter are not included as did not present with significant correlations in either PVD cohorts.
CTEPH: chronic thromboembolic pulmonary hypertension; CTED: chronic thromboembolic disease; 6MWD: six-minute walk distance; 6MWW: 6-minute walk work; (n): number of patients who had that measurement in the population; RA: right atrial; mmHg: millimetres per mercury; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; EDP: end diastolic pressure; CO: cardiac output; [TD]: thermal dilution; CI: cardiac index, litres per minute per square metre; PVR: pulmonary vascular resistance; dyn.s.cm^{-5}: dynes pascal seconds per cubic meter; TPG: transpulmonary pressure gradient; FEV1: forced expiratory volume in 1 s; VC max.: maximal vital capacity; FEV1: forced expiratory volume in 1 s; VC max.: maximal vital capacity; KCO: transfer coefficient; TLC: total lung capacity; IC: inspiratory capacity; LVIDd: left ventricular internal dimension-diastole; LVIDs: left ventricular internal dimension-systole; cm: centimetres; LV mass: left ventricular mass; SV (LVOT): stroke volume (left ventricular outflow tract); mL/min^2: millimetres/minute squared; TAPSE: tricuspid annular plane systolic excursion; RA: right atrium.

physiologist who provided no verbal encouragement. 6MWD was recorded, and 6MWW was calculated as product of 6MWD × bodyweight (in kg). 6MWD data was excluded from the data collection if patients' walking performance was limited by external factors such as arthritis.

PFT

PFT was performed on the MS-PFT Pro (Vyaire UK Ltd). Transfer factor for carbon monoxide (TLCO) was measured by the single-breath technique, and values recorded were not corrected for haemoglobin values. Lung volumes were determined by body plethysmography. PFTs were conducted by the physiologist according to ATS/ERS guidelines.[16–18] Lung function parameters collected for review were as follows: maximal vital capacity (VC) or forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), TLCO, Transfer coefficient (KCO), total lung capacity (TLC) and inspiratory capacity (IC).

RHC

A Swan-Ganz catheter was used for hemodynamic measurements in resting supine position, and haemodynamic parameters were determined by the thermal dilution technique and indirect Fick technique based on Fick's principle (COFick = oxygen uptake/(arterial oxygen concentration–venous oxygen concentration). Haemodynamic results were calculated from a mean of a minimum of three measurements.

Echocardiogram

Echocardiograms were performed and analysed by British Society of Echocardiography (BSE)-accredited cardiac physiologists and Clinical Scientists upon Philips Epiq cardiac ultrasound machines (Koninklijke Philips, Netherlands), following standard BSE protocols. Echocardiographic parameters collected for review reflected left ventricular (LV) size (internal diameter in diastole and systole, LVIDd and LVIDs, respectively), LV function (SV and SV indexed to body surface area, both from LV outflow tract method (SV (LTOT), SVi), LV structure (mass), right ventricular (RV) function (tricuspid annual plane systolic excursion (TAPSE) and RV size (basal diameter) right atrium area (RA).

Statistical analysis

Data was presented as mean $\pm$ SD or median or median (interquartile range) based on outcome of Shapiro-Wilk normality test. Statistical analysis was performed on Statistical Packages for Social Sciences version 26. Pearson or Spearman rank, depending on data distribution, was used to determine the correlation coefficients of clinical test parameters, relationship to peak VO_2, VE/VCO_2 and O_2 pulse.

Linear regression analysis was performed to investigate the ability to predict peak VO_2 from the clinical test parameters. Those parameters with the highest correlation coefficient, as well as those most clinically measured in that population group, were selected to enter into the regression model to produce the equation to estimate peak VO_2 for the different PVD populations. Equations were produced to predict peak VO_2 based on patients CPET data performed at baseline on 41 CTEPH patients and 38 CTED patients up to January 2019. The remaining cohort who performed CPET post this date was used to validate the produced equations to determine the validity of the equations at predicting peak VO_2. Additionally, the equations were validated on any patients who performed serial CPET results post baseline which were not used in the original regression analysis. This allowed determination of the validity of the equations at predicting a patient's future peak VO_2 result, which has significance in determination as often patients with PVD perform serial CPET tests over time to detect changes in exercise capacity. The validation was done by calculating estimated peak VO_2 using the predictive equations and comparing to peak VO_2 obtained from the CPET in this cohort. Additionally, for the validation of peak VO_2 measurement to account for patient size, the peak VO_2 values were converted to percent predicted. The validation method used to compare the level of agreement between measured and estimated peak VO_2 was the Bland Altman method.

Results

Exercise characteristics of population

In both CTEPH and CTED cohorts, mean (SD) percent predicted peak VO_2 was 75.2 ± 21 and 93 ± 20, respectively, and reduced peak VO_2 (<80% predicted) was presented in 30 and 9 patients, respectively. In the CTEPH and CTED cohorts, mean (SD) percent predicted peak O_2 pulse was 80 ± 20.1 and 88.4 ± 18.5, respectively, and reduced O_2 pulse (<80% predicted) was presented in 27 and 13 patients, respectively. In both CTEPH and CTED cohorts, median VE/VCO_2 slope was 45 (13) and 34.7 (9), respectively, and with elevated VE/VCO_2 slope (>35) presented in 59 and 22 patients, respectively.

Correlation of clinical parameters to peak VO$_2$ (mL/min)

In total, 117 patients had performed a 6MWT, 94 of which had undergone PFT, 84 patients had undergone RHC and 117 patients had undergone an echocardiogram within a 60-day time period of their CPET performed, and this data was correlated to CPET data. Additionally, in total, 40 of the patients had performed serial CPETs over this time period and also were included in the presented correlations.

It was demonstrated that 6MWD had a moderate relationship to peak VO_2 in both CTEPH (r = 0.62) and CTED (r = 0.62) (both p < 0.001, see Fig. 1a). The relationship strengthened when accounting for bodyweight in both CTEPH (r = 0.83) and CTED (r = 0.77) (both p < 0.001), see Fig. 1b). TLCO was strongly associated with peak VO_2 in both CTEPH (r = 0.80) and CTED (r = 0.83) (both p < 0.001), see Fig. 1c).

The stronger relationship of 6MWW to peak VO_2 was observed according to both corridor size lengths for the 6MWT (Supplement Table 2). Results demonstrated slightly stronger correlational relationship between 6MWW and 6MWD to peak VO_2 with 10-m corridor length compared with 30 m corridor length. The cohort size performing the 30-m 6MWT was considerably smaller in comparison to the cohort sizes performing the 10-m 6MWT. This smaller cohort size is a likely impacting factor on the smaller correlation coefficient presented between peak VO_2 and 30m 6MWT data.

Additionally, a number of haemodynamic, pulmonary function and echocardiogram parameters presented with significant association to peak VO_2, and this data is presented in Table 1.

Prediction equations for peak VO$_2$

Predictive equations were produced for peak VO_2 mL/min in both CTEPH and CTED, and this was based upon parameters presenting with the highest correlation coefficients and being most clinically measured in that population group.
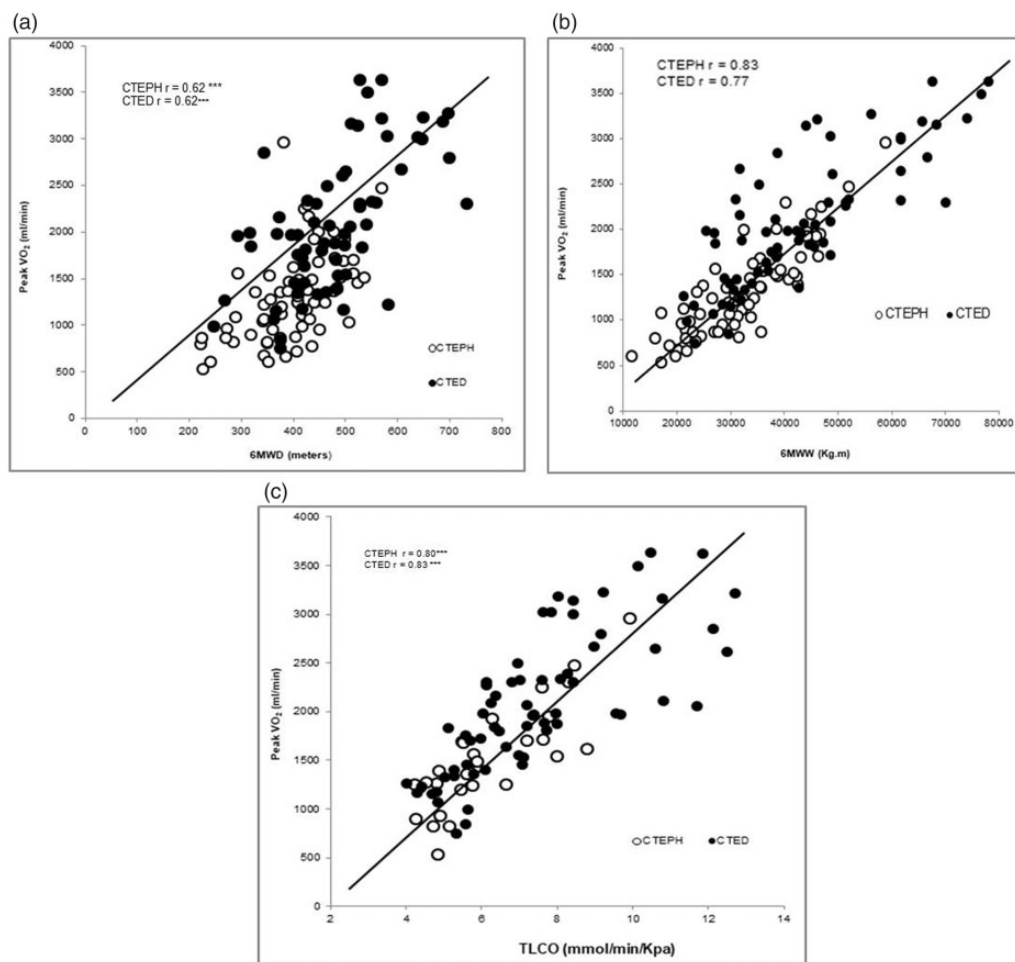
Fig. 1. The correlational relationship between peak VO2 to 6MWD, 6MWW and TLCO.

The predictive equation produced in CTEPH was based on data collected on a cohort of 41 patients. In this cohort, 6MWW presented with the highest correlation coefficient of $(r = 0.89)$ and was selected to be entered into the regression model. To note, TLCO presented with the next highest correlation coefficient $(r = 0.82)$ but was not used alongside 6MWW in the model, as this measure was not recorded in the whole of this cohort. 6MWW incorporated into the regression model accounted for 79% variance in peak VO_2 mL/min and with the equation as follows: predicted peak VO_2 mL/min $= -252 + 0.049$ (6MWW) $(F = 132.5$, $p < 0.001$, R squared $= 0.79$, standard error of estimate $= 250$ mL/min.

For the CTED group, the production of the predictive equation was based on the cohort of 38 patients. 6MWW and TLCO were the parameters most clinically measured in this cohort and additionally presented with the highest correlation coefficients of $r = 0.79$ and $r = 0.76$, respectively. 6MWW and TLCO were incorporated into the regression model and accounted for 78% variance in peak VO_2 mL/ min with the equation as follows: predicted peak VO_2 mL/ min $= -266 + 0.028(6MWW) + TLCO(147.6)$ $(F = 73.4$,

$p < 0.001$, adjusted R squared $= 0.78$, standard error of estimate $= 313$ mL/min.

Validation of predictive equations for peak VO$_2$

Bland Altman analysis was used to validate the predictive equations. Bland Altman was used to compare calculated peak VO_2 from the predictive equation compared to peak VO_2 obtained from the CPET. Additionally, for validation for comparison, peak VO_2 values were converted to percent predicted values.

The predictive equations were validated in 22 CTEPH patients who performed CPET post January 2019. In addition, the equation was validated on subsequent serial CPET results from 13 patients from the original cohort in which these results were not used in the original regression model. Whereas in the CTED population, the predictive equations were validated in 13 patients who performed CPET post January 2019 and additionally in 15 patients who were from the original cohort.

Fig. 2a presents in the CTEPH population the demonstrated mean bias was 36.1 mL/min $\pm$ 303 mL/min between

Table 2. Correlation coefficients of clinical parameters to peak oxygen pulse.

	CTEPH	CTED
Six-minute walk test parameters		
6MWW (kg.m)	**0.79*** (n = 68)**	**0.72*** (n = 66)**
6MWD (m)	**0.53*** (n = 68)**	**0.57*** (n = 66)**
Haemodynamic parameters		
Systolic pulmonary pressure (mmHg)	**−0.67*** (n = 31)**	0.14 (n = 22)
mPAP (mmHg)	**−0.47*** (n = 63)**	0.31 (n = 34)
EDP (mmHg)	0.11 (n = 57)	**0.40* (n = 33)**
CO [TD] (L/min)	**0.33** (n = 62)**	**0.67*** (n = 33)**
CI [TD] (L/min^2)	0.03 (n = 43)	**0.66*** (n = 28)**
PVR [TD] (dyn.s.cm^{-5})	**−0.61*** (n = 54)**	−0.15 (n = 28)
CO [Fick] (L/min)	**0.41** (n = 42)**	**0.76*** (n = 34)**
CI [Fick] (L/min^2)	0.02 (n = 41)	**0.46* (n = 25)**
TPG (mmHg)	**−0.57*** (n = 50)**	0.28 (n = 20)
Pulmonary function test parameters		
FEV1 (L)	**0.41* (n = 31)**	**0.61*** (n = 67)**
VC max (L)	**0.55** (n = 31)**	**0.69*** (n = 67)**
TLCO (mmol/min/KPa)	**0.69*** (n = 31)**	**0.81*** (n = 67)**
KCO (mmol/min/KPa/L)	−0.07 (n = 31)	**0.31* (n = 67)**
TLC (L)	**0.52** (n = 26)**	**0.65** (n = 52)**
IC (L)	**0.71*** (n = 25)**	**0.74*** (n = 52)**
Echocardiogram parameters		
LVIDd (cm)	**0.61*** (n = 64)**	**0.64*** (n = 69)**
LVIDs (cm)	**0.44*** (n = 61)**	**0.49*** (n = 62)**
LV mass (g)	**0.56*** (n = 64)**	**0.62*** (n = 62)**
SV (LTOT) (mL)	**0.35** (n = 61)**	**0.55*** (n = 58)**
SV (index) (mL/min^2)	−0.02 (n = 59)	**0.31* (n = 53)**
RV basal diameter (cm)	−0.07 (n = 58)	**0.37** (n = 59)**
RA area (cm^2)	−0.21 (n = 48)	**0.60*** (n = 49)**

Note: Significant correlation coefficient (r) are highlighted in bold and significance level presented with * (***p < 0.001; **p < 0.0l*; p < 0.05). Note that RA pressure, PCWP and TAPSE are not included as did not present with significant correlations in either PVD cohorts.

(n): number of patients who had that measurement in the population; CTEPH: chronic thromboembolic pulmonary hypertension; CTED: chronic thromboembolic disease; 6MWD: six-minute walk distance; 6MWW: six-minute walk work; kg.m: kilograms.meters; FEV1: forced expiratory volume in 1 s; VC max.: maximal vital capacity; FEV1: forced expiratory volume in 1 s; TLCO: transfer factor for carbon monoxide mmol/min/kPa; KCO: transfer coefficient; TLC: total lung capacity; IC: inspiratory capacity; RA: right atrial; mmHg: millimetres per mercury; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; EDP: end diastolic pressure; CO: cardiac output; [TD]: thermal dilution; CI: cardiac index, litres per minute per square metre; PVR: pulmonary vascular resistance; dyn.s. cm^{-5}: dynes pascal seconds per cubic meter; TPG: transpulmonary pressure gradient; LVIDd: left ventricular internal dimension-diastole; LVIDs: left ventricular internal dimension-systole; cm: centimetres; LV mass: left ventricular mass; SV (LVOT): stroke volume (left ventricular outflow tact); mL/min^2: millimetres/minute squared; TAPSE: tricuspid annular plane systolic excursion; RV basal dia.: right ventricular basal diameter; RA: right atrium.

measured peak VO_2 from the CPET compared to calculated peak VO_2. When comparing percent predicted values, the bias between percent predicted peak VO_2 and calculated predicted peak VO_2 was $3.6 \pm 19\%$ as shown in Fig. 2b.

Fig. 3a presents in the CTED population the demonstrated mean bias 19 mL/min $\pm$ 393 mL/min between measured peak VO_2 from the CPET compared to estimated peak VO_2. When comparing percent predicted values, the demonstrated bias between percent predicted peak VO_2 and calculated predicted peak VO_2 was $1.4 \pm 18\%$ as shown in Fig. 3b.

Peak oxygen pulse

6MWW and TLCO demonstrated a high association to peak oxygen pulse. The correlation of 6MWW to peak oxygen pulse in CTEPH was $r = 0.79$ and in CTED was

$r = 0.72$ ($p < 0.001$) see Fig. 4a. Additionally, TLCO had a high association with peak oxygen pulse in both CTEPH ($r = 0.69$) and CTED ($r = 0.81$) ($p < 0.001$) see Fig. 4b.

Additionally, a number of haemodynamic, pulmonary function and echocardiogram parameters presented with significant association to peak oxygen pulse, and these are presented in Table 2.

VE/VCO$_2$ slope

A number of parameters presented with significant association to VE/VCO$_2$ and are presented in Table 3.

Discussion

In PVD, the significant key exercise abnormalities presented on a CPET include a reduction in exercise capacity (peak
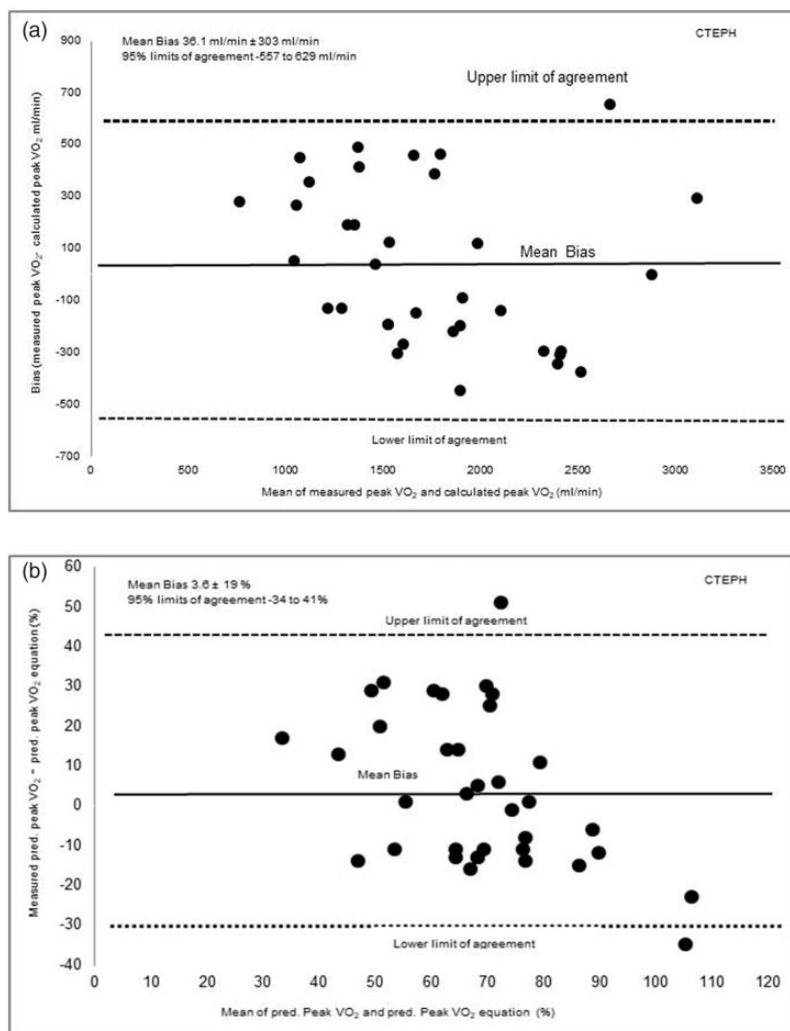
Fig. 2. (a) The level of agreement (bias) between measured peak VO_2 (mL/min) achieved performing the CPET compared to calculated peak VO_2 estimated using the equation in the CTEPH population. (b) The level of agreement in predicted peak percentage VO_2 (%) measured from the CPET compared to calculated predicted peak VO_2 (%) from the equation in the CTEPH population. Presented as mean bias and upper and lower limits of agreement calculated as $1.96 \times SD$ of the bias.

VO_2), reduction in O_2 pulse due to SV impairment and ventilation–perfusion mismatching as presented by an elevated VE/VCO₂. We therefore determined the association of 6MWW and other clinical test parameters to these key CPET parameters in patients with CTEPH and CTED.

Exercise capacity in PVD is commonly assessed using the 6MWT. Our investigation demonstrated 6MWD to only have a significant moderate relationship to peak VO_2 in both CTEPH and CTED populations and for the correlation to strengthen to a high relationship when accounting for bodyweight, i.e. the 6MWW. This is similar to previous investigations which have demonstrated a more superior relationship between 6MWW and peak VO_2 in PAH patients.[1,6,8] A limitation with the 6MWD measurement is that it does not account for body habitus and therefore does not account for the associated metabolic and cardiovascular expenditure of exercise. Our findings demonstrate that

accounting for body habitus strengthens the relationship to peak VO_2.

A number of clinical parameters were found to correlate with peak VO_2 in our cohort of patients, with TLCO presenting with one of the greatest associations. A proportion of the PVD cohort exhibited a reduction in TLCO, this abnormality likely occurring in PVD due to reductions in pulmonary blood flow and membrane diffusing capacity.[19] TLCO represents the exchanges of gases between the lungs and the pulmonary circulation and a reduction in TLCO would therefore be expected to reduce exercise capacity. We are unaware of any previous investigations into the association of TLCO to peak VO_2 in PVD. In PAH, a higher degree of TLCO impairment has found to be associated with lower 6MWD,[20] and furthermore, pre-operative TLCO has been shown to be the sole independent predictor of exercise intolerance after pulmonary endarterectomy.[21]
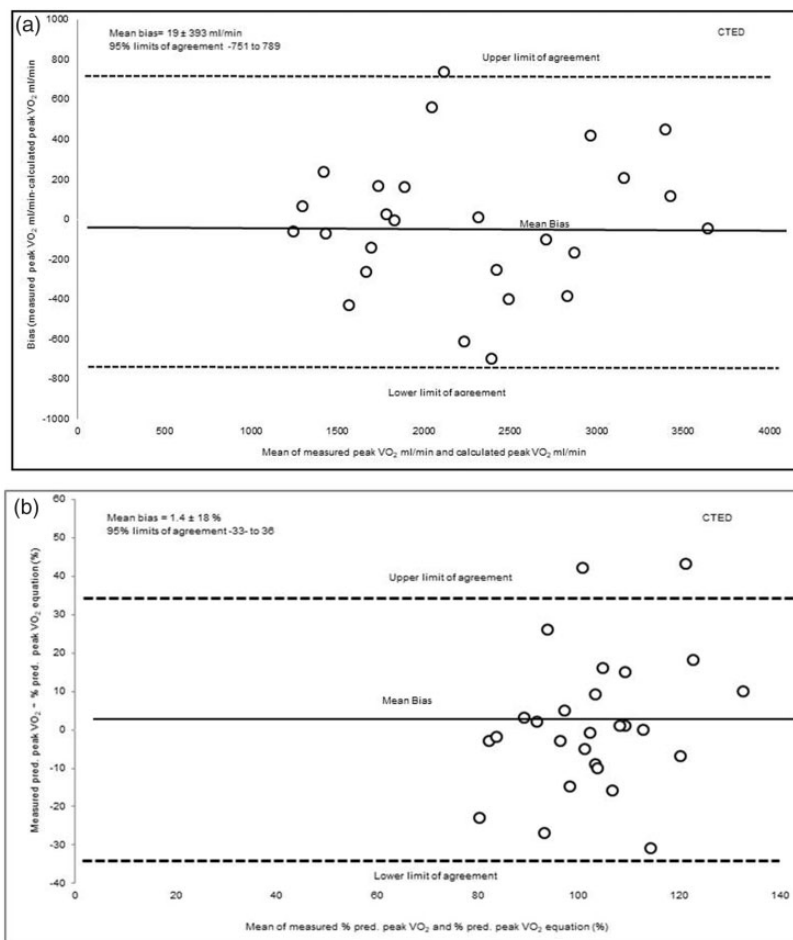
Fig. 3. (a) The level of agreement (bias) between measured peak VO$_2$ (mL/min) achieved performing the CPET compared to calculated peak VO$_2$ estimated using the equation in the CTED population. (b) The level of agreement in predicted peak percentage VO$_2$ (%) measured from the CPET compared to calculated predicted peak VO$_2$ (%) from the equation in the CTED population. Presented as mean bias and upper and lower limits of agreement calculated as $1.96 \times$ SD of the bias.

In our CTEPH cohort, numerous haemodynamic parameters were found to associate correlate to peak VO$_2$. Pulmonary vascular resistance (PVR), systolic pressure and mPAP demonstrated the greatest negative association to peak VO$_2$. These parameters reflect the severity of right heart dysfunction and remodelling of the pulmonary vasculature which would impact exercise capacity negatively. In the CTED cohort, in to whom present with exhibit normal resting haemodynamics, resting CO was the parameter best associated with peak VO$_2$ with a moderate association demonstrated. On echocardiogram, parameters reflecting left ventricular size and structure such as LVIDd and LV mass demonstrated the best association to peak VO$_2$ with a positive moderate association. Meyer et al.[22] similarly demonstrated a relationship between exercise capacity and LV size dimensions. Additionally, other factors such as oxygen use by peripheral tissues and muscle factors have been found to be related to exercise intolerance in PVD. A recent study by Tobita et al.[23] demonstrated that in CTEPH, patient's peak VO$_2$ was influenced by both

arterio-venous oxygen content differences (a-vO$_2$ difference) muscle factors such as quadriceps strength in addition to haemodynamic factors. Due to the retrospective nature of this study design, peripheral factors such as a-vO$_2$ difference and muscles parameters were not measured in our cohorts. Peripheral factors such as a-vO$_2$ difference and muscle parameters should be further explored in future investigations alongside other clinical parameters such as 6MWW and TLCO in relation to exercise intolerance in PVD.

Predictive equations were produced to estimate peak VO$_2$ in our CTEPH and CTED cohorts. In the CTEPH cohort, 6MWW explained 79% variance in peak VO$_2$. Whereas in the CTED cohort, both 6MWW and TLCO explained 78% of the variance in peak VO$_2$. Despite the high R squared values suggesting that high variance in peak VO$_2$ could be explained, our validation of predictive equations did not demonstrate a consistent prediction across the cohorts. The Bland Altman analysis demonstrated a variable bias of 36.1 ± 303 mL/min and 19 ± 393 mL/min in CTEPH and CTED cohorts, respectively
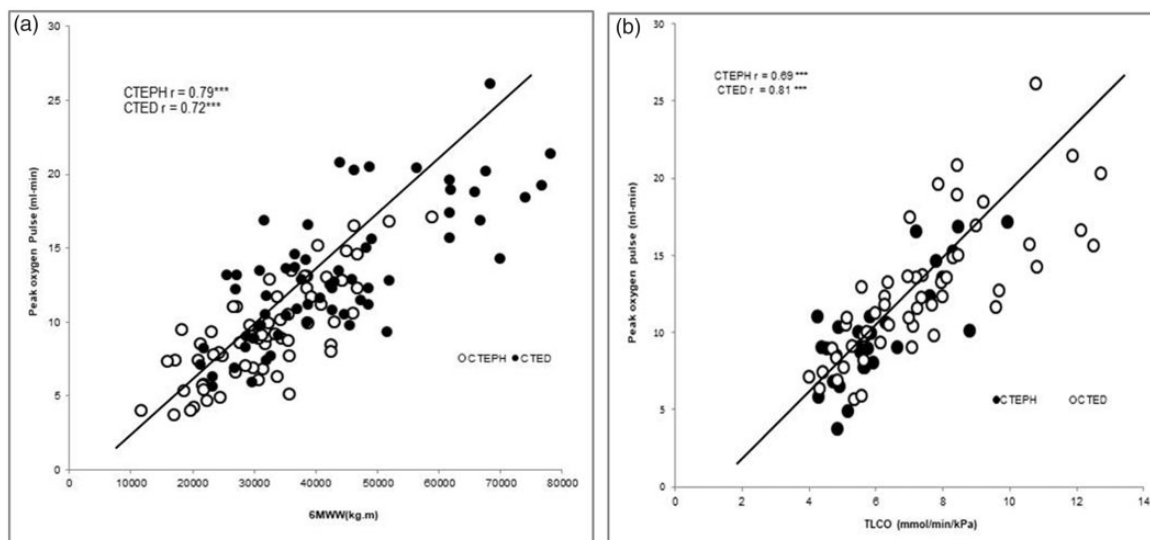
Fig. 4. The correlational relationship between peak oxygen pulse to 6MWW and TLCO.

(see Figs. 3a and 4a). This variable bias means in a proportion of the population the difference between predicted peak VO_2 and estimated peak VO_2 would be clinically significant different. Our findings therefore indicate that 6MWW and TLCO were strongly associated to peak VO_2, but these parameters incorporated in our equations were unable to predict peak VO_2 values accurately across the entire cohorts. Therefore, our predictive equations may have limited clinical applicability. Further investigation is needed to clarify the predictive ability of clinical parameters such as 6MWW, TLCO and other factors in predicting peak VO_2.

In PVD, limitation of O_2 pulse limitation presentation can occur due to reduced ability of the right ventricle to increase SV. In our PVD cohort, a proportion presented with this limitation with predicted O_2 pulse ranging between 32 and 132%. A number of parameters correlated to peak O_2 pulse. 6MWW demonstrated the highest association to peak O_2 pulse in the CTEPH cohort and similarly presented a high relationship in the CTED cohort. TLCO demonstrated the highest association to peak O_2 in the CTED cohort.

To highlight, 6MWW and TLCO were similarly the highest associated parameters to peak VO_2 in these cohorts. This similar association could perhaps be expected, as according to the Fick equation peak VO_2 is greatly determined by the heart, increasing CO and therefore is likely to be greatly associated to peak O_2 pulse capability as a surrogate for SV. Walking performance can be predictive of maximal CO, as with exercise there is an increased linear relationship between CO and O_2 consumption. Therefore, with increase work and therefore walking speed can be considered an indirect measure of the heart's ability to increase output with exercise and reflect maximal CO.[24] The high relationship of 6MWW to peak O_2 demonstrated by our findings suggests accounting body weight as well as 6MWD could better reflect maximal CO and thus exercise capacity. The

clinical value and utility of 6MWW in PVD are yet to be fully determined and need to be determined. If 6MMW is able to better reflect maximal CO compared with 6MWD, which our findings may suggest, it could have better discriminative capacity at detecting clinical change following therapeutic changes and prognostic value. A limitation with the 6MWT is its inability to identify meaningful clinical change in patients with a better functional status and in these patients CPET can serve this role more. CO and TLCO can be closely inter-related in increasing gas exchange during exercise as with exercise increases in TLCO can be greatly dependent on increases in CO which increases pulmonary capillary blood volume and thus gas exchange.[25] This inter-relationship could explain the good association of peak O_2 pulse to TLCO.

Both CTEPH and CTED cohorts had raised VE/VCO_2 at peak exercise, 45 and 35, respectively. Held et al.[26] also demonstrated similarly elevated VE/VCO_2 slope values in both CTEPH and CTED cohorts, a common sign of PVD. This occurs in PVD due to ventilation–perfusion mismatching as a result of reduced lung perfusion. In the CTEPH population, haemodynamic parameters better reflected VE/VCO_2 with a number of haemodynamic parameters significantly associated with VE/VCO_2 notably which were amongst the highest correlated to VE/VCO_2. Previous investigations have shown a moderate to low relationship of VE/VCO_2 to PVR in PAH and in CTEPH[10–12] and moderate relationship of TPG to VE/VCO_2 in PAH.[12] PVR could be expected to reflect VE/VCO_2, as increased PVR means that CO cannot adequately increase during exercise. This will cause reduced perfusion of the lungs and increased dead space ventilation causing raised ventilation-perfusion mismatching. TPG values, a measure of the driving pressure through the pulmonary capillary network, therefore can be reflective of

Table 3. Correlation coefficients of clinical parameters to VE/VCO2 slope.

	CTEPH	CTED
Six-minute walk test parameters		
6MWW (kg.m)	−0.30 (n=66)	**−0.52*** (n=64)**
6MWD (m)	**−0.29* (n=66)**	**−0.26* (n=64)**
Haemodynamic parameters		
Systolic pulmonary pressure (mmHg)	**0.52** (n=29)**	−0.04 (n=22)
mPAP (mmHg)	**−0.47*** (n=63)**	−0.12 (n=34)
EDP (mmHg)	−0.12 (n=55)	**−0.36* (n=33)**
CO [TD] (L/min)	−0.17 (n=60)	**−0.43* (n=33)**
CI [TD] (L/min^2)	0.01 (n=41)	**−0.60** (n=28)**
PVR [TD] (dyn.s.cm^{-5})	**0.69*** (n=53)**	0.14 (n=27)
CO [Fick] (L/min)	−0.16 (n=40)	**−0.54** (n=34)**
CI [Fick] (L/min^2)	0.05 (n=39)	**−0.42* (n=25)**
TPG (mmHg)	**0.66*** (n=50)**	−0.13 (n=20)
Pulmonary function test parameter		
VC max (L)	−0.16 (n=30)	**−0.27* (n=65)**
TLCO (mmol/min/KPa)	**−0.42*(n=30)**	**−0.62*** (n=65)**
KCO (mmol/min/KPa/L)	−0.24 (n=30)	**−0.52***(n=65)**
IC (L)	−0.38 (n=24)	**−0.46** (n=50)**
Echocardiogram parameters		
LVIDd (cm)	**0.61*** (n=64)**	**−0.33** (n=63)**
LVIDs (cm)	**0.44*** (n=61)**	**−0.32* (n=61)**
LV mass (g)	−0.25 (n=62)	**−0.32* (n=61)**
SV (LVOT) (mL)	−1.0 (n=59)	**−0.42** (n=56)**
TAPSE (cm)	**−0.29* (n=61)**	**−0.34** (n=62)**
RV basal diameter (cm)	**0.34* (n=56)**	−0.13 (n=58)
RA area (cm^2)	−0.22 (n=48)	**0.38** (n=46)**

Note: Significant correlation coefficient (r) are highlighted in bold and significance level presented with * (***p < 0.001; **p < 0.01; *p < 0.05).
Note that RA pressure, PCWP, FEV₁, TLC, SV index, PCWP and TAPSE are not included as did not present with significant correlations in either PVD cohorts.
(n): number of patients who had that measurement in the population; CTEPH: chronic thromboembolic pulmonary hypertension; CTED: chronic thromboembolic disease; 6MWD: six-minute walk distance; 6MWW: six-minute walk work; kg.m: kiolograms.meters; FEV1: forced expiratory volume in 1 s; VC max.: maximal vital capacity; FEV1: forced expiratory volume in 1 s; TLCO: transfer factor for carbon monoxide mmol/min/kPa; KCO: transfer coefficient; TLC: total lung capacity; IC: inspiratory capacity; RA: right atrial; mmHg: millimetres per mercury; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; EDP: end diastolic pressure; CO: cardiac output; [TD]: thermal dilution; CI: cardiac index, litres per minute per square metre; PVR: pulmonary vascular resistance; dyn.s.cm^{-5}: dynes pascal seconds per cubic meter; TPG: transpulmonary pressure gradient; LVIDd: left ventricular internal dimension-diastole; LVIDs: left ventricular internal dimension-systole; cm: centimetres; LV mass: left ventricular mass; SV (LVOT): stroke volume (left ventricular outflow tact); mL/min^2: millimetres/minute squared; TAPSE: tricuspid annular plane systolic excursion; RV basal dia.: right ventricular basal diameter; RA: right atrium.

maintaining gas exchange during exercise.[25] In the CTED cohort, TLCO was the parameter most reflective of VE/VCO₂ demonstrating a moderate inverse relationship, and similarly in the CTEPH cohort, a moderate relationship was also demonstrated but of a lesser strength. Other investigations in other cohorts have shown associations between TLCO and VE/VCO₂ in other cohorts.[27,28] This could be due to higher TLCO allowing for better maintenance of gas exchange at lower ventilation costs.[29]

This study has a number of limitations. Our PVD cohort consisted of CTEPH and CTED patients and therefore our findings may not be applicable to a PAH cohort due to the different pathophysiology and disease characteristics. Future investigations should explore associations in this PH subgroup. Furthermore, not every clinical parameter was measured in each patient within the timeframe around CPET; therefore, associations could not be determined for every parameter for all patients.

To conclude, a number of clinical test parameters correlated to CPET parameters in our CTEPH and CTED populations. Our findings highlighted that 6MWW and TLCO were the most strongly correlated to peak VO₂, but from our produced predictive equations, we were unable to predict peak VO₂ values accurately across our cohorts. Therefore, our predictive equations may have limited clinical applicability. 6MWW demonstrated a high relationship to both VO₂ and peak O₂ pulse and therefore may be a good indirect indicator of maximal CO. Future investigations are needed to determine the clinical value of 6MWW by determining its sensitivity in detecting clinical change following therapy compared with 6MWD and other CPET parameters and determine its prognostic value.

Authors' contribution

LCR-study design, data analysis collection, drafting on manuscript and approval. KEO- study design, drafting on manuscript and approval. AJF- study design, data analysis collection, drafting on manuscript and approval. KPS- study design, drafting on manuscript and approval. No ethical approval or subject consent for study as was retrospective.

Conflict of interest

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Supplemental Material

Supplemental material for this article is available online.

References

1. Mainguy V, Malefant S, Neyron A, et al. Alternatives to the six-minute walk test in pulmonary arterial hypertension. *PLoS One* 2014; 9: e103626.

2. Demir R and Kucukoglu MS. Six minute walk test in pulmonary arterial hypertension. *Anatol J Cardiol* 2015; 15: 245–254.

3. Weatherald J, Farina S and Bruno N, et al. Cardiopulmonary exercise testing in pulmonary hypertension. *Ann Am Thorac Soc* 2017; 14: 84–92.

4. Schwaiblmair M, Faul C, Schedit WV, et al. Ventilatory efficiency testing as prognostic value in patients with pulmonary hypertension. *BMC Pulm Medc* 2012; 12: 12–23.

5. Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60: 1192–1201.

6. Oudiz RJ, Barst RJ and Hansen JE, et al. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. *Am J Cardiol* 2006; 97: 123–126.

7. Zapacio AG, Fuentes D and Rojo-Tirado MA, et al. Predicting peak oxygen uptake from the 6-minute walk test in patients with pulmonary hypertension. *J Cardiopulm Rehabil Prev* 2016; 36: 203–208.

8. Deboeck G, Niset G and Vachiery JL, et al. Physiological response to the six-minute walk test in pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 667–672.

9. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/ American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1447–1478.

10. Tsuboi Y, Tanaka H, Nishio R, et al. Associations of exercise tolerance with hemodynamic parameters for pulmonary arterial hypertension and for chronic thromboembolic pulmonary hypertension. *J Cardiopulm Rehabila Prev* 2017; 37: 341–346.

11. Ptaszyńska K, Kopczyńska A, Krentowskab A, et al. The strengths and weaknesses of non-invasive parameters obtained by echocardiography and cardiopulmonary exercise testing in comparison with the hemodynamic assessment by the right heart catheterization in patients with pulmonary hypertension. *Adv Med Sci* 2017; 62: 39–44

12. Correale M, Tricarico L, Ferraretti A, et al. Cardiopulmonary exercise test predicts right heart catheterization. *Eur J Clin Invest* 2017; 47: doi: 10.1111/eci.12851.

13. Borlaug BA, Kane GC, Melenovsky V, et al. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2016; 43: 3293–3302.

14. Gläser S, Itterman T, Schäper C, et al. The Study of Health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing. *Pnemologie* 2013; 67: 58–63.

15. Bongers B, Hulzebos HJ, Brussel MV, et al. *Pediatric norms for cardiopulmonary exercise testing. In relation to gender and age.* 1st ed. London: Boxpress, 2012.

16. Graham BL, Steenbruggen I and Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med* 2019; 200: 70–88.

17. Graham BL, Brussaco V, Burgos F, et al. ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017; 49: 1600016.

18. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511–522

19. Low AT, Medford ARL, Millar AB, et al. Lung function in pulmonary hypertension. 2015. *Resp Med* 2015; 109: 1224–1249.

20. Kacprzak A, Szturmowicz M, Franczuk M, et al. Clinical meaning of low DLCO in idiopathic pulmonary arterial hypertension (IPAH) – prospective single centre study. *Eur Respir J* 2015; 46: PA2117.

21. Ruigrok D, Lilian D, Meijboom J, et al. Persistent exercise intolerance after pulmonary endarterectomy for CTEPH. *Eur Respir J* 2020; 57: 2000109.

22. Meyer M, McEntee RK, Nyotowidjojo I, et al. Relationship of exercise capacity and left ventricular dimensions in patients with a normal ejection fraction. An exploratory study. *PLos One* 2015; 10: e0119432.

23. Tobita K, Goda A, Nishida Y, et al. Factors contributing to exercise capacity in chronic thromboembolic pulmonary hypertension with near-normal haemodynamics. *J Heart Lung Transplant* 2021; 40: 677–686.

24. Deboeck G, Taboada D, Hagan G, et al. Maximal cardiac output determines 6 minutes walking distance in pulmonary hypertension. *PloS One* 2014; 9: e92324.

25. Coffman KE, Curry TB, Dietz NM, et al. The influence of pulmonary vascular pressures on lung diffusing capacity during incremental exercise in healthy aging. *Physiol Rep* 2018; 6: e13565.

26. Held M, Kolb P, Grün M, et al. Functional characterization in patients with chronic thromboembolic disease. *Respiration* 2016; 91: 503–509.

27. Lalande S, Yerly P, Faoro V, et al. Pulmonary vascular distensibility predicts aerobic capacity in healthy individuals. *J Physiol* 2012; 590: 4279–4288.

28. Faoro V, Deboeck G, Vicenzi M, et al. Pulmonary vascular function and aerobic exercise capacity at moderate altitude. *Med Sci Sports Exerc* 2017; 49: 2131–2138.

29. Faoro V and Forton K. *Pulmonary vascular reserve and aerobic exercise capacity*. London: IntechOpen, 2019.