Distinguishing Pulmonary Hypertension in Interstitial Lung Disease by Ventilation and Perfusion Defects Measured by Cardiopulmonary Exercise Testing

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Key Words

Cardiopulmonary exercise test · Interstitial lung disease · Lung transplantation · Pulmonary hypertension · Ventilation/perfusion defects

Abstract

Background: Pulmonary hypertension (PH) is common in interstitial lung disease (ILD). Since cardiopulmonary exercise testing (CPET) is useful in understanding the pathophysiology of respiratory disorders and can distinguish between ventilation and perfusion (V/Q) defects, it may have a role in the detection of PH in ILD. We evaluated whether CPET can detect PH through analysis of V/Q defects in ILD. **Objectives:** We aimed to use CPET to determine if there are changes in the ventilation and the activity pattern of mixed-expired carbon dioxide pressure (PECO₂) and end-tidal carbon dioxide pressure (PetCO₂) in ILD patients with and without PH. **Methods:** A retrospective chart review was done of all patients who received lung transplants at the Columbia University Medical Center between 2000 and 2011 with the diagnosis of ILD. CPETs were performed during the 2 years prior to transplantation; right heart catheterizations and pulmonary function tests were performed within 4 months of CPET. **Results:** The ILD patients with PH demonstrated significantly

lower PetCO₂ and PECO₂ during certain levels of exercise with a distinctive activity pattern for PECO₂/PetCO₂. **Conclusions:** Evaluation of V/Q defects through the PECO₂ and PetCO₂ patterns on CPET in ILD patients can distinguish between patients with and without PH.

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Introduction

Interstitial lung disease (ILD) often leads to pulmonary hypertension (PH) through mechanisms of pulmonary arteriolar vasoconstriction, vascular remodeling, inflammation and destruction due to progressive parenchymal architectural distortion, perivascular fibrosis, thrombotic angiopathy and associated left-sided cardiac disease [1, 2].

Hansen et al. [3] have previously shown that ventilation/perfusion (V/Q) mismatch caused by airway defects could be differentiated from perfusion defects using non-invasive measures of mixed-expired carbon dioxide pressure (PECO₂) and end-tidal carbon dioxide pressure (PetCO₂) in heart failure, primary PH, and chronic obstructive lung disease patients. Since cardiopulmonary exercise testing (CPET) is often useful in understanding

the pathophysiology of respiratory disorders [4], prior studies have assessed how to determine the domain and mechanism of these diseases, particularly when two disorders such as PH and ILD might coexist [3]. In addition to the actual values of PECO_2 and PetCO_2 , the activity pattern of PECO_2 to PetCO_2 was shown to differ as patients go through the stages of exercise-rest, unloaded pedaling, ventilatory threshold (VT), and peak performance. The differences in activity patterns can be striking when looking at the phases of exercise to allow for separation of patients based on their underlying physiology when plotted. We hypothesized that there may be similar changes in ventilation and the activity pattern of PECO_2 to PetCO_2 in patients with ILD that may be helpful in distinguishing between patients with and without PH.

The main objective of this study was to determine if PECO_2 , PetCO_2 , $\text{PECO}_2/\text{PetCO}_2$, and the activity pattern of PECO_2 versus PetCO_2 could differentiate between abnormal V/Q due to ventilatory disorders alone and abnormal V/Q caused by airway and perfusion disorders during increasing work rates in severe ILD patients with and without PH.

Patients and Methods

Patients

A retrospective chart review was performed of all patients who received a lung transplant at the Columbia University Medical Center between December 2000 and September 2011 with the diagnosis of ILD, and who had CPETs during the 2 years prior to transplantation and right heart catheterizations (RHCs) and pulmonary function tests (PFTs) performed within 4 months of CPET. Patients with known left heart failure, known cardiac disease, ischemic or valvular heart disease determined by echocardiography, nuclear cardiology study, or left heart catheterization and RHC were excluded. Further reasons for exclusion included missing or incomplete CPETs and RHCs or testing far from the transplant date; RHCs done outside of our hospital, or a mean pulmonary arterial pressure ≥ 25 with a mean pulmonary capillary wedge pressure (mPCWP) > 15 . Subjects were verified to have ILD according to the diagnostic criteria established by the American Thoracic Society (ATS)/European Respiratory Society [5]. The Institutional Review Board of the New York Presbyterian-Columbia University Medical Center approved this study.

Cardiopulmonary Exercise Testing

CPET was performed on an electronically braked cycle ergometer (Ergometrics 800; SensorMedics Inc., Yorba Linda, Calif., USA) with a Viasys Encore Metabolic Cart (Viasys Corporation, Loma Linda, Calif., USA); prior to 2005, a SensorMedics Vmax 229 series workstation was used. The equipment was calibrated prior to every test. Continuous 12-lead telemetry was monitored via CardioSoft electrocardiogram software (GE/CardioSoft, Houston, Tex., USA); prior to 2005, a model Max-1 electrocardiogram was

used (Marquette Medical Systems, Milwaukee, Wisc., USA). The exercise protocol was ramping and followed the exercise protocol used in the National Emphysema Treatment Trial [6] and ATS guidelines [7, 8]. An individualized ramping protocol was determined by the maximal voluntary ventilation (MVV) test. Individuals who achieved ≤ 40 l/min MVV performed a 5-watt per minute ramping protocol, and those attaining > 40 l/min MVV performed a 10-watt ramping protocol. Oxygen was administered if used daily or with exercise at $30.00 \pm 0.20\%$ via a closed system; all calibrations were two-point calibrations with hyperoxic and hypoxic points and included hypercarbic and absent carbon dioxide levels of calibration. The metabolic system was validated for use with hyperoxic testing and was stable for measurement of fraction of expired carbon dioxide at hyperoxic situations. CPET variables were collected breath by breath and included the rate of carbon dioxide production by weight (VCO_2 in ml/kg/min), maximal oxygen consumption by weight (VO_2 in ml/kg/min), percent of predicted VO_2 ($\text{VO}_2\%$), minute ventilation (VE ; in l/min), tidal volume (VT ; in liters), respiratory exchange ratio, and PetCO_2 (in mm Hg). The predicted watts and $\text{VO}_2\%$ were calculated for males and females as described by Jones et al. [9]. Each VT was determined independently by three exercise physiologists and then averaged. PECO_2 was calculated as a result of dividing 863 by the VE/VCO_2 ratio [3].

Pulmonary Function Tests

All PFTs were performed according to the ATS criteria [10]. This included the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), residual volume (RV), total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DLCO), and forced expiratory flow (FEF). Percentages of predicted FEV_1 ($\text{FEV}_1\%$), FVC ($\text{FVC}\%$), DLCO ($\text{DLCO}\%$), TLC ($\text{TLC}\%$), and FEF ($\text{FEF}\%$) were calculated for males and females as described in prior publications [11–13]. Arterial blood gases were taken at rest and included arterial oxygen pressure (PaO_2) and acidity.

Right Heart Catheterization

Catheterization was performed at rest with a Swan-Ganz catheter. PH was defined as mean pulmonary arterial pressure ≥ 25 mm Hg at rest with a normal mPCWP (≤ 15) [14, 15]. Other variables collected included mean right arterial pressure, mean mPCWP, cardiac output, and cardiac index when available in the chart.

Statistics

Normal distribution was assessed using the Kolmogorov-Smirnov test. Variables that were normally distributed are presented as means $\pm$ SD or as mean percent of predicted $\pm$ SD. Variables that deviated from normal are presented as medians and interquartile ranges (25–75%). Between-group comparisons were performed using unpaired Student *t* or the Mann-Whitney *U* test for normal and nonnormal data, respectively. Equal distribution was not assumed. A χ^2 test was used to analyze 2×2 tables. Analysis of variance was used to determine significant differences between time periods with the Gabriel post hoc test. Receiver-operating characteristic analyses were used to find sensitivities and specificities. Both univariate and multivariate analyses were performed to determine variables associated with PH. All analyses were completed using SPSS version 19 (SPSS, Chicago, Ill., USA). All tests were two tailed; statistical significance was set at $p \leq 0.005$, and 95% confidence intervals were determined.

Table 1. Baseline characteristics, hemodynamic values and PFT parameters

Patient characteristics	ILD, PH (n = 25)	ILD, no PH (n = 50)	p value
Age, years	57±8	60±7	0.125
Females, %	32	42	0.402
Body mass index	28.4±4.7	26.8±3.4	0.142
FVC%	51 (44–66)	46 (37–57)	0.138 ^a
FEV ₁ %	54±14	52±15	0.621
TLC% ^b	54±15	51±16	0.389
DLCO% ^c	20±6	31±14	<0.001
RV/TLC ^b	0.29 (0.19–0.39)	0.35 (0.31–0.41)	0.045 ^a
FEF 25–75%	72±43	85±43	0.222
FEF 25%	70±26	75±29	0.441
mPAP, mm Hg	33.7±7.6	18.9±4.2	<0.001
mRAP, mm Hg ^d	4.8±4.0	2.3±2.6	0.008
mPCWP, mm Hg ^e	7.7±4.2	6.4±3.6	0.196
Cardiac output, l/min ^f	4.6±1.3	5.1±1.3	0.169
Cardiac index, l/min/m ² ^g	2.4±0.7	2.7±0.6	0.088
Time between CPET and RHC, days	2 (–10 to 37)	2 (–8 to 4)	0.258 ^a

Means ± SD and medians (interquartile ranges). Values in bold indicate significance. RV = Residual volume; mPAP = mean pulmonary arterial pressure; mRAP = mean right atrial pressure.

^a Mann-Whitney U test.

^b Five patients with PH and 7 patients with no PH did not have RV/TLC or TLC% available.

^c Two patients with PH and 9 patients with no PH did not have DLCO% available.

^d One patient with no PH did not have mRAP available.

^e One patient with PH did not have mPCWP available.

^f Five patients with PH and 4 patients with no PH did not have cardiac output available.

^g Eight patients with PH and 6 patients with no PH did not have cardiac index available.

Results

Between December 2000 and September 2011, there were 175 lung transplantations for ILD. A total of 75 patients with ILD who met the inclusion criteria were analyzed. There were 42 patients with idiopathic pulmonary fibrosis, 5 with sarcoidosis, 12 with parenchymal lung disease, 8 with hypersensitivity pneumonitis, and 8 with fibrosis due to connective tissue disease. Patient demographic, hemodynamic, and PFT parameters are shown in table 1. According to hemodynamic criteria, 34% of the patients were classified as having PH. Age, sex, and body mass index distributions were similar between those with and without PH. Except for DLCO, the PFT parameters were similar between the two groups.

The CPET parameters for both groups are presented in table 2. All patients with PH and 90% of patients without PH were on supplemental oxygen during CPET ($p = 0.161$). There were no differences in the fraction of inspired oxygen (FIO_2) between those with and without PH ($p = 0.687$). The mean FIO_2 for the 70 patients tested on

supplemental oxygen was 30.00 ± 0.023 . There were no significant differences in CPET variables between those on and off supplemental oxygen.

Figure 1a shows the PECO_2 values for the two groups at each of the four activity stages. The PH group significantly differed from the no PH group during the unloaded, VT, and peak stages. Those without PH significantly increased their PECO_2 from rest to each level of exercise; from rest to unloaded $p = 0.008$, from rest to VT $p < 0.001$, and from rest to peak $p < 0.001$. Those with PH did not significantly change their PECO_2 .

Figure 1b shows the PetCO_2 values for the same activity stages for both groups. The two groups differed significantly during rest, unloaded pedaling, and peak exercise. Neither group significantly changed its PetCO_2 from rest.

Figure 1c shows the $\text{PECO}_2/\text{PetCO}_2$ ratios for the activity stages in both groups. Surprisingly, the groups were not significantly different in any of the activity stages as compared to the Hansen study. Those with PH significantly increased their $\text{PECO}_2/\text{PetCO}_2$ ratio between rest

Table 2. CPET parameters in ILD patients, comparing those with and without PH

CPET variable	ILD, PH (n = 25)	ILD, no PH (n = 50)	p value
Peak $\dot{V}O_2$, ml/kg/min	13.88±3.63	16.02±4.88	0.037
Peak $\dot{V}O_2\%$	53±14	61±17	0.034
VT $\dot{V}O_2$, ml/kg/min	10.82±2.60	12.79±3.54	0.020
VT $\dot{V}O_2\%$	40±9	49±13	0.003
Peak $\dot{V}CO_2$, ml/kg/min	13.16±3.42	16.58±4.79	0.001
VT $\dot{V}CO_2$, ml/kg/min	9.66±2.03	11.89±3.29	0.002
Peak $\dot{V}E$, l/min	51±13	47±14	0.248
Peak $\dot{V}E/\dot{V}CO_2$	45 (40–50)	36 (32–43)	<0.001^a
VT $\dot{V}E/\dot{V}CO_2$	46.82±10.84	39.08±7.24	0.011
Peak $PECO_2$	18.46±4.11	23.30±5.03	<0.001
VT $PECO_2$	19.12±3.25	22.78±3.93	0.001
Peak $PetCO_2$	28.56±7.72	37.85±7.12	<0.001
VT $PetCO_2$	31.73±7.21	37.16±6.31	0.010
Peak $PECO_2/PetCO_2$	0.66±0.08	0.62±0.10	0.090
Base SpO_2	96 (94–98)	97 (95–98)	0.496 ^a
Peak SpO_2	89 (85–94)	91 (89–94)	0.219 ^a
Base V_d/V_T^b	0.39±0.08	0.41±0.07	0.245
Peak V_d/V_T^b	0.29±0.07	0.31±0.09	0.468
Peak breathing reserve, %	20±41	28±41	0.454
Peak V_T , liters	1.10 (0.80–1.35)	0.90 (0.68–1.20)	0.193 ^a
Peak RER	1.00 (0.80–1.00)	1.00 (0.90–1.20)	0.016 ^a
Time from CPET to LTx, days	222±185	233±140	0.787

Means ± SD and medians (interquartile ranges). Values in bold indicate significance. There are 18 patients with PH and 43 without PH who have ventilatory threshold (VT) measurements available. SpO_2 = Oxygen saturation; V_d = dead space; RER = respiratory exchange ratio; LTx = lung transplantation.

^a Mann-Whitney U test.

^b V_d/V_T is estimated from $PetCO_2$.

Table 3. Univariate analysis of PH

Patient characteristics	p value	Hazard ratio	95% confidence interval	
			lower limit	upper limit
DLCO%	<0.001	0.826	0.743	0.918
PaO_2	0.977	1.000	0.984	1.016
6-min walk distance	0.009	0.998	0.997	1.000
$\dot{V}E/\dot{V}CO_2$ rest	0.027	1.055	1.0006	1.106
$\dot{V}E/\dot{V}CO_2$ unloaded	0.009	1.075	1.018	1.035
$\dot{V}E/\dot{V}CO_2$ VT	0.009	1.117	1.028	1.214
$\dot{V}E/\dot{V}CO_2$ peak	0.005	1.070	1.021	1.122
$PECO_2$ rest	0.032	0.840	0.716	0.985
$PECO_2$ unloaded	0.008	0.817	0.714	0.948
$PECO_2$ VT	0.004	0.760	0.632	0.915
$PECO_2$ peak	0.001	0.804	0.709	0.912
$PetCO_2$ rest	0.001	0.854	0.777	0.940
$PetCO_2$ unloaded	0.001	0.859	0.787	0.938
$PetCO_2$ VT	0.009	0.885	0.807	0.970
$PetCO_2$ peak	<0.001	0.848	0.779	0.923

and peak exercise ($p < 0.001$). The group without PH significantly increased their $PECO_2/PetCO_2$ ratio from rest to each level of exercise; from rest to unloaded $p = 0.001$, from rest to VT $p < 0.001$, from rest to peak $p < 0.001$, and from unloaded to peak $p = 0.005$.

Next we performed univariate and multivariate analyses with known variables that are associated with PH, namely DLCO [16–18], 6-min walk distance [18–21], PaO_2 [17], and $\dot{V}E/\dot{V}CO_2$ [22, 23] along with $PECO_2$ and $PetCO_2$. We chose to only perform univariate analyses on $PECO_2$ and $PetCO_2$ since the $PECO_2/PetCO_2$ ratio did not show any difference between activity stages. The results of the univariate analyses (table 3) reveal that $PECO_2$ had the most significant and strong hazard ratios at all activity levels.

In the multivariate analysis, we used two main models. The first model included either $PECO_2$ (at rest, unloaded, VT, or peak), $PetCO_2$ (at rest, unloaded, VT, or peak) or $PECO_2$ and $PetCO_2$ (at rest, unloaded, VT, or peak) with DLCO%, 6-min walk distance, and PaO_2 with $\dot{V}E/\dot{V}CO_2$ at

Fig. 1. Values for subjects with ILD with and without PH (PH vs. no PH) during ramping cycle ergometry tests at rest, unloaded pedaling, VT and peak exercise. Values are means and 95% confidence intervals. * $p < 0.005$.

VT. The second model included these variables but used VE/VCO_2 at peak instead of at VT. None of the multivariate analyses showed $PECO_2$ or $PetCO_2$ to be significant at the $p \leq 0.005$ level. However, in the model with VE/VCO_2 at peak, $PetCO_2$ at peak had a significance of $p = 0.037$ with a hazard ratio of 0.845 (95% confidence intervals: 0.722–0.990); when both $PECO_2$ at rest and $PetCO_2$ at rest were entered, $PetCO_2$ had a significance of $p = 0.038$ with a haz-

ard ratio of 0.806 (95% confidence intervals: 0.658–0.988), $PECO_2$ was not significant. Interestingly, in every model, $DLCO\%$ was significant at least at the $p \leq 0.05$ level, while no other variables were significant.

When the pattern of activity for $PECO_2$ to $PetCO_2$ was plotted (fig. 2), there was a distinctive activity pattern for patients with PH versus those without PH. Those without PH showed a progressive increase, while those with PH

Fig. 2. Figure depicts the PCO₂ values for ILD patients with and without PH (PH vs. no PH) during ramping cycle ergometry tests at rest, unloaded pedaling, VT and peak exercise. Each group has a distinctive activity pattern.

demonstrated a bowed appearance with reversion to the left. Subgroup analysis by diagnosis for those diagnoses with more than 2 patients (idiopathic pulmonary fibrosis, nonspecific fibrotic lung disease, and connective tissue-associated ILD) showed preservation of this pattern (plots not shown). Receiver-operating characteristic analysis revealed that a peak PECO₂ of 22.59 had a sensitivity of 0.920 and a specificity of 0.667 while a peak PetCO₂ of 39.10 had a sensitivity of 0.920 and a specificity of 0.479.

Discussion

This study demonstrated that there were clear ventilatory differences between severe ILD patients evaluated for lung transplantation who had PH and those who did not have PH. Patients with PH had lower PetCO₂ and PECO₂ values with higher VE/VCO₂ ratios, as would be anticipated [16]. Although there were no clear differences between the PECO₂/PetCO₂ ratios, there was a distinctive pattern of activity for PECO₂ versus PetCO₂ for patients with PH versus those without PH.

The lower values of PetCO₂ and PECO₂ throughout exercise in the patients with PH compared to those without PH are similar to the known ventilatory inefficiencies seen in patients with pulmonary vascular limitations [3]

and suggest an inability to increase pulmonary perfusion in exercise. Supporting that perfusion is mainly involved are the findings that ventilation and dead space/VT were not different between the two groups. The fact that neither those with nor those without PH were able to significantly decrease their PetCO₂ above the VT reflects a similar difficulty in increasing ventilation in response to lactic acidemia [3]. In ILD patients without PH, all levels of exercise had a higher PECO₂ than at rest, while those with PH did not significantly change their PECO₂. This may suggest an alteration in ventilation that is exaggerated in patients with PH. Notably, the lower VCO₂ values in patients with PH may possibly indicate worse lung function. Additional support for this finding is the relationship between DLCO% and PH. The lack of change in the PECO₂/PetCO₂ ratios may reflect the relative relationship of the changes in ventilation, with both the PetCO₂ and PECO₂ moving in similar directions in all ILD patients.

The interesting finding is that the pattern of activity of PECO₂ versus PetCO₂ seen in our group of patients with ILD is similar to published data from Hansen et al. [3]. ILD patients without PH showed a progressive increase in PECO₂ versus PetCO₂ values going from rest to peak exercise. This pattern is similar to and in the same range of values described for patients with chronic obstructive pulmonary disease (a gradual mild increase) in their study. In contrast, for patients with ILD and PH, the values showed a bowed appearance with reversion to the left, a pattern similar to the values seen in patients with primary PH in the Hansen study. These similarities between the pattern of activity of PECO₂ versus PetCO₂ and the results of published data in patients with isolated lung disease and isolated primary PH indicate that the pattern of activity of PECO₂ to PetCO₂ may be sensitive for detecting the presence of V/Q mismatching due to PH in ILD. Further evidence for this can be seen in the PFTs. There were no significant differences in the FEF 25–75%, FEF 25% or RV/TLC ratio between those with and without PH. This indicates that the alteration in V/Q matching is due to perfusion changes and not due to other associated ventilatory alterations such as the presence of small airway obstruction/distortion.

There are several limitations to this study, including its retrospective nature and the relatively smaller numbers of subjects, which also did not allow for complete analysis based on diagnostic subgroups. Some of the subjects were tested on room air, and this may have introduced a degree of error and also increased the standard deviations of the data, limiting the sensitivity of the study to detect more

subtle changes. However, this was adjusted for through the use of $\dot{V}CO_2$, and $\dot{V}O_2$ was not a main outcome of our study. The analysis of the pattern of activity of $\dot{P}ECO_2$ to $\dot{P}etCO_2$ is also somewhat limited because quantification of these values is somewhat difficult. We did not collect arterial blood gases with exercise so $PaCO_2$ or pH measurements could not be used in order to detect changes in dead space/ $\dot{V}T$.

In conclusion, the ventilation of patients evaluated for transplantation with ILD and PH is different from that of patients with ILD but no PH. There are unique patterns of activity of $\dot{P}ECO_2$ versus $\dot{P}etCO_2$ for one group of patients versus the other. Further elaboration of the activity pattern with objectification of the findings may

help to distinguish the presence of perfusion defects caused by PH from the ventilatory limitations in patients with ILD.

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The authors have no conflicts of interest.

References

- 1 Strange C, Highland KB: Pulmonary hypertension in interstitial lung disease. *Curr Opin Pulm Med* 2005;11:452–455.
- 2 Polomis D, Runo JR, Meyer KC: Pulmonary hypertension in interstitial lung disease. *Curr Opin Pulm Med* 2008;14:462–469.
- 3 Hansen JE, Ulubay G, Chow BF, Sun XG, Wasserman K: Mixed-expired and end-tidal CO_2 distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest* 2007;132:977–983.
- 4 ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.
- 5 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
- 6 Group NETT: A randomized trial comparing lung volume reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
- 7 American Thoracic Society, American College of Chest Physicians: ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–277.
- 8 Wasserman K, Hansen J, Sue D, Stringer W, Whipp B: Principles of Exercise Testing and Interpretation, ed 3. Philadelphia, Lippincott Williams & Wilkins, 1999.
- 9 Jones N, Makrides L, Hitchcock C, Chypchar T, McCartney N: Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;131:700–708.
- 10 Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson D, MacIntyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G: Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–522.
- 11 Crapo R, Morris A, Clayton P, Nixon C: Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir* 1982;18:419–425.
- 12 Crapo R, Morris A, Gardner R: Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–664.
- 13 Crapo R, Morris A: Standardized single-breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981;123:185–189.
- 14 Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, ESC Committee for Practice Guidelines (CPG): Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–2537.
- 15 Badesch DB, Champion HC, Gomez Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A: Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S55–S66.
- 16 Boutou AK, Pitsiou GG, Trigonis I, Papakosta D, Kontou PK, Chavouzis N, Nakou C, Argyropoulou P, Wasserman K, Stanopoulos I: Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. *Respirology* 2011;16:451–458.
- 17 Launay D, Mouthon L, Hachulla E, Pagnoux C, de Groote P, Remy-Jardin M, Matran R, Lambert M, Queyrel V, Morell-Dubois S, Guillemin L, Hattron P-Y: Prevalence and characteristics of moderate to severe pulmonary hypertension in systemic sclerosis with and without interstitial lung disease. *J Rheumatol* 2007;34:1005–1011.
- 18 Pitsiou G, Papakosta D, Bouros D: Pulmonary hypertension in idiopathic pulmonary fibrosis: a review. *Respiration* 2011;82:294–304.
- 19 Andersen CU, Mellemkjaer S, Hilberg O, Nielsen-Kudsk JE, Simonsen U, Bendstrup E: Pulmonary hypertension in interstitial lung disease: prevalence, prognosis and 6 min walk test. *Respir Med* 2012;106:875–882.
- 20 Leuchte HH, Neurohr C, Baumgartner R, Holzapfel M, Giehl W, Vogeser M, Behr J: Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med* 2004;170:360–365.
- 21 Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF: Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006;129:746–752.
- 22 Dumitrescu D, Oudiz RJ, Karpouzas G, Hovanesyan A, Jayasinghe A, Hansen JE, Rosenkranz S, Wasserman K: Developing pulmonary vasculopathy in systemic sclerosis, detected with non-invasive cardiopulmonary exercise testing. *PLoS One* 2010;5:e14293.
- 23 Arena R, Guazzi M, Myers J, Grinnan D, Forman DE, Lavie CJ: Cardiopulmonary exercise testing in the assessment of pulmonary hypertension. *Expert Rev Respir Med* 2011;5:281–293.