Factors predicting pulmonary hypertension in idiopathic pulmonary fibrosis patients

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Context Pulmonary hypertension (PH) is a common complication of idiopathic pulmonary fibrosis (IPF) and an important pathophysiologic mechanism of exercise intolerance and poor quality of life in these patients.

Aims The aims of this study were to assess predictors of PH in IPF from both resting pulmonary function test (PFT) and cardiopulmonary exercise testing (CPET) parameters and to establish cut-off values from resting PFT and CPET parameters for the prediction of PH.

Settings and design This was a randomized, double-blind, and prospective study.

Patients and methods Thirty-five patients with stable IPF were assessed in terms of resting pulmonary functions, arterial blood gases (ABG), echocardiography, and incremental CPET. Patients were classified into a PH group and a non-pulmonary-hypertension group.

Statistical analysis Both groups were compared in terms of resting PFT and CPET parameters. A receiver operating characteristic curve was constructed to establish cut-off values for the prediction of PH.

Results PH was observed in 13 (37.14%) patients. There were no significant differences between both groups in age and sex. forced vital capacity (FVC)%, forced expiratory volume in one second (FEV_1)%, inspiratory capacity, resting and exercise partial arterial oxygen tension (PaO_2) and arterial oxygen saturation (SaO_2), and oxygen consumption (VO_2%) were significantly reduced in the PH group, whereas the dyspnea score, resting and exercise $PaCO_2$, respiratory frequency, and minute ventilation were significantly increased in the PH group. The receiver operating characteristic curve showed that resting SaO_2 of 92.9% or less and exercise SaO_2 of 87% or less had sensitivity of 84.6, and 100%, and specificity of 90.9 and 81.8%, respectively.

Conclusion Marked deterioration in resting PFT, exercise parameters, and SaO_2 can predict PH in IPF patients.
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Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease characterized by progressive scarring of the lung tissue and a restrictive pattern of lung function with reduced gas exchange capacity [1]. Pulmonary arterial hypertension has been defined as a mean pulmonary artery pressure (mPAP) 25 mmHg or more at rest, with a normal pulmonary capillary wedge pressure [2]. The prevalence of pulmonary hypertension (PH) in patients referred for lung transplantation is 32–46%, but the overall prevalence of PH in IPF is lower than that in patients referred for transplantation [3]. In patients with IPF without PH, pulmonary function tests (PFTs) are used for the evaluation of severity and progression of disease [4]. Although respiratory failure is the most common cause of death in IPF, several comorbidities may also play a role; PH is the most important comorbidity with a prognostic role [5]. PH may reduce life expectancy in IPF to less than 1 year [5]. Studies using echocardiography for assessment of mortality in IPF showed that systolic pulmonary artery pressure (sPAP) more than 50 mmHg is associated with a median survival of 0.7 years; however, it is 4.1 years for an sPAP of 36–50 mmHg and 4.8 years for an sPAP of 35 mmHg or less [6].

Objectives

The aims of this work were to assess predictors of PH in IPF from both resting PFT and cardiopulmonary exercise testing (CPET) parameters and to determine cut-off values from resting PFT and CPET parameters to predict PH in IPF.

Patients and methods

The present study was carried out in the Department of Chest Diseases, Faculty of Medicine, Assiut University Hospital. Thirty-five patients with IPF were included in this study.

The diagnosis of IPF was made on the basis of the high resolution CT chest (HRCT) chest criteria according to ATS/ERS/JRS/ALAT, 2011 statement [7]. All patients were subjected to a full assessment of medical history, general and local chest examination, chest

radiograph postroanterior chest radiograph (PA) view, HRCT chest, and spirometry.

Spirometry was performed using (Cosmed SrL, Quark PFT Ergo, P/N Co9035-12-99; Italy), where predicted values for FEV_1/FVC, FEV_1, FVC, and inspiratory capacity (IC), were calculated. Incremental CPET was performed using (Cosmed SrL, Quark PFT Ergo, P/N Co9035-12-99), where gas exchange values and exercise parameters were collected breath by breath, allowing measurement of minute ventilation (VE), tidal volume (VT), respiratory frequency (RF), oxygen uptake (VO_2), end-tidal carbon dioxide ($PETCO_2$), the anaerobic threshold, oxygen pulse (VO_2/HR), ventilatory equivalent for carbon dioxide at anaerobic threshold, and the breathing reserve.

The level of dyspnea was assessed at the beginning of CPET and at VO_2 using the Borg Rating of Perceived Exertion Scale [8]. The Borg rating uses a scale from 0 to 10; the patient rates his/her perception of dyspnea, for example, scale 0 means no dyspnea, 3 means moderate dyspnea, scale 7 means severe dyspnea, but the patient can continue exercise, and scale 10 means maximum dyspnea such that the patient terminates exercise.

Lung volumes and diffusion capacity of the lung for carbon monoxide were determined using the single-breath method (D97723, Zan 300; Oberthulba, Germany, CO/CH_4 analyzer), where the total lung capacity (TLC) was calculated and predicted values for diffusing capacity for carbon monoxide (DLCO) adjusted for hemoglobin concentration were measured.

ABG in room air were obtained both at rest and at the end of exercise. A blood sample was obtained from the radial artery and analyzed using a blood gas analyzer (Rapid lab 850; CHIRON/Diagnostics Halstead, UK), with calculation of PaO_2, SaO_2, and $PaCO_2$.

Two-dimensional Doppler echocardiography was performed using (Philips Invisor, 2002; Philips, USA). The mPAP was calculated from sPAP using the Chemla formula: mPAP = 0.61 × sPAP + 2 mmHg [9]. Patients were classified into two groups: PH patients, in whom mPAP was 25 mmHg or more, and a non-pulmonary-hypertension (NPH) group, in whom mPAP was less than 25 mmHg.

Statistical analyses

All PFT and exercise parameters are presented as mean percent predicted (%Pred) ±SD. The PH and NPH groups were compared in terms of resting PFT and CPET parameters using a *t* sample test, where *P* value less than 0.05 was considered significant. A receiver operating characteristic (ROC) curve was used to establish a cut-off value for prediction of PH in IPF patients.

Results

On comparing clinical and ABG parameters between PH and NPH groups, there were no significant differences in age and sex, dyspnea level, and arterial $PaCO_2$ both at rest and exercise, and VO_2 max was significantly higher in the PH group; however, arterial oxygen both at rest and exercise was significantly lower in the PH group (Tables 1 and 2).

Comparison between both groups for the resting PFT showed that PH patients had lower FEV_1%, FVC%, and IC%, whereas there was no significant difference in DLCO and TLC% (Table 3).

CPET patients with PH had significantly lower VO_2 max and VT, and had significantly higher VE/VCO_2, VE, and RF (Table 4).

The ROC curve (Fig. 1) was used for different parametrs to detect a cut-off value for predicting PH, and it was found that resting SaO_2 92.9% or less and exercise SaO_2 87% or less had sensitivity of 84.6 and 100% and specificity of 90.9 and 81.8%, respectively, with area under the curve 0.858 for resting SaO_2 and 0.958 for exercise SaO_2.

Discussion

PH is a common complication of IPF as a result of progressive fibrosis and honeycomb changes with destruction of pulmonary vasculature and hypoxic pulmonary vasoconstriction [10]. In our study, comparison between IPF patients with and without PH showed that oxygen tension and saturation reduced significantly in PH patients, and on constructing an ROC curve (Fig. 1) to establish a cut-off value, resting SaO_2 less than 92.9% had sensitivity of 84.6% and specificity of 90.9%, and exercise SaO_2 less than 87% had a sensitivity of 100% and a specificity of 81.8%. Many studies support our results. Hamada *et al.* [11] reported that hypoxia is a frequent consequence of PH; they found a significant correlation between resting PaO_2 and mPAP in IPF ($r = -0.47$, $P < 0.001$). Also, intermittent nocturnal hypoxia for a long duration may play a significant role in the development of disproportionate PH [11]. Agarwal *et al.* [12] documented that fibrosis in IPF leads to entrapment of segments of pulmonary vasculature and thrombosis, with resulting fibrosis. These changes result in hypoxia, which leads to pulmonary vasoconstriction with permanent structural changes in pulmonary blood vessels, even those far from areas of fibrosis [12]. Shorr *et al.* [13] reported that $PaCO_2$ in IPF patients with mild to moderate PH was higher compared with those with normal pulmonary artery pressure; this is consistent with our results. Assessment of dyspnea

Table 1 Comparison between both groups in resting clinical and arterial blood gases parameters

Parameters	NPH (*n* = 22)	PH (*n* = 13)	*P* value
Sex [*N* (%)]			0.868
Male	7 (31.8)	3 (23.1)	
Female	15 (68.2)	10 (76.9)	
Age	51.77 ± 9.23	45.15 ± 13.67	0.096
Resting Borg scale	1.59 ± 1.18	3.08 ± 1.61	0.004*
Resting PaO_2	73.23 ± 11.05	61.54 ± 10.34	0.004*
Resting SaO_2	95.06 ± 1.86	91.36 ± 3.08	0.000*
Resting $PaCO_2$	34.99 ± 4.09	42.09 ± 9.56	0.004*

NPH, non-pulmonary-hypertension; PH, pulmonary hypertension; value below 0.05 for *P* value is significant.

Table 2 Comparison between both groups in postexercise clinical and arterial blood gases parameters

Parameters	NPH (*n* = 22)	PH (*n* = 13)	*P* value
Postexercise Borg scale	3.73 ± 3.17	6.62 ± 3.53	0.018*
Postexercise PaO_2	59.41 ± 11.37	46.38 ± 4.43	0.000*
Postexercise SaO_2	89.79 ± 3.87	81.04 ± 3.99	0.000*
Postexercise $PaCO_2$	35.50 ± 5.56	43.35 ± 10.99	0.008*

NPH, non-pulmonary-hypertension; PH, pulmonary hypertension; value below 0.05 for *P* value is significant.

Table 3 Comparison between pulmonary hypertension and non-pulmonary-hypertension patients in resting pulmonary function parameters pulmonary function test

Parameters	NPH (*n* = 22)	PH (*n* = 13)	*P* value
FEV/FVC	79.18 ± 7.90	80.39 ± 7.82	0.665
FVC (%)	67.00 ± 13.31	50.23 ± 13.05	0.001*
FEV_1 (%)	63.43 ± 16.22	45.95 ± 15.16	0.003*
DLCO	47.77 ± 18.38	40.38 ± 19.12	0.266
TLC (%)	72.41 ± 11.73	68.92 ± 16.04	0.464
IC (%)	69.73 ± 23.06	43.32 ± 21.73	0.002*

IC, inspiratory capacity; NPH, non-pulmonary-hypertension; PH, pulmonary hypertension; TLC, total lung capacity; value below 0.05 for *P* value is significant.

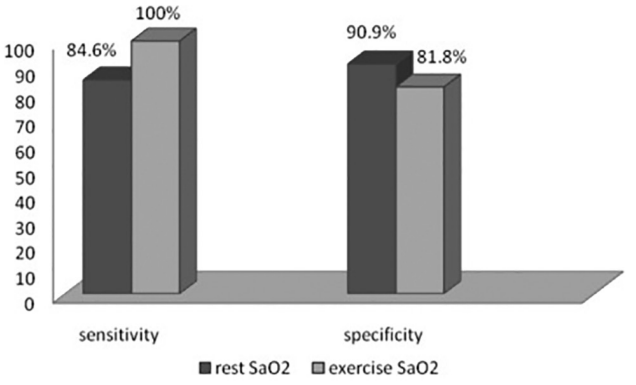
Table 4 Cardiopulmonary exercise testing parameters in pulmonary hypertension and non-pulmonary-hypertension patients

Parameters	NPH (*n* = 22)	PH (*n* = 13)	*P* value
VO_2%	55.00 ± 15.59	43.38 ± 10.57	0.023*
VE/VCO_2	35.23 ± 10.92	51.38 ± 15.17	0.001*
VT	0.96 ± 0.17	0.78 ± 0.21	0.008*
VE (l/min)	38.07 ± 7.17	45.15 ± 11.95	0.035*
RF	40.50 ± 7.96	46.49 ± 6.01	0.025*

NPH, non-pulmonary-hypertension; RF, respiratory frequency; VE, minute ventilation; VE/VCO_2 ventilatory equivalent for CO_2; VO_2, maximum oxygen consumption; VT, tidal volume; *P* value < 0.05 is significant.

using the Borg scale both at rest and during exercise was higher in the PH group compared with NPH patients. Gläser *et al.* [14] studied the impact of PH on gas exchange and exercise capacity in patients with

Fig. 1



Sensitivity and specificity of resting SaO_2 92.9% or less and exercise SaO_2 87% or less for predicting pulmonary hypertension in idiopathic pulmonary fibrosis patients.

pulmonary fibrosis and confirmed our results as they observed a mean score of 3 for patients without PH and 6 for patients with PH ($P < 0.05$).

Comparison of resting PFT showed that each of FEV_1%, FVC%, and IC% reduced significantly in PH patients, whereas there were no significant differences in DLCO% and TLC%. Although Gläser *et al.* [14] documented that except for diffusing capacity, PFT showed no significant differences between both groups, Shorr *et al.* [13] observed that FEV_1 was lower in patients with PH (50.0 ± 16.5 vs. 52.7 ± 16.5% predicted, $P < 0.0001$) and FEV_1 was significantly correlated with mPAP. Also, Agarwal *et al.* [12] found a statistically significant difference in PaO_2 levels and FVC in patients with PH compared with NPH patients, and a significant association was observed between the presence of decreasing FVC and hypoxemia and the development of PH in IPF patients. Javier and Sicilian [15] observed that FVC was significantly positively correlated with IC%; thus, we can predict that IC decreased in PH patients as observed in our study. Although many studies have documented that DLCO decreased significantly in PH patients [14], our study found that DLCO decreased in the PH group compared with the NPH group, but not significantly differently; correcting DLCO for alveolar volume will results in significant difference between both groups. CPET evaluation of IPF patients showed that VO_2% and VT reduced significantly in the PH group; meanwhile, VE/VCO_2, RF, and VE reduced significantly in the NPH group. The results of Gläser *et al.* [14] were in agreement with ours as they observed that peak VO_2 was significantly lower in patients with PH, and the ventilatory inefficiency (VE/VCO_2) slope was significantly pronounced in patients with PH. They reported that hyperventilation causes increased VE/VCO_2 slope and this is the result of a reduced pulmonary capillary bed with shortened red blood cell

transit times and thus impaired oxygenation, and also increased functional intrapulmonary right to left shunt. Javier and Sicilian [15] studied lung function, breathing pattern, and gas exchange in interstitial lung disease and observed that lower values of FVC were associated with an increased RF and decreased VT, and in our study, PH patients had lower values for FVC in comparison with NPH patients. Javier and Sicilian [15] reported that possible mechanisms of rapid shallow breathing are the mechanical effects of increased lung elastance, perceived as increasing load by mechanoreceptors, and stimulation of intrapulmonary receptors, for example, J receptors.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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