Respiratory Medicine (2009) **103**, 1136–1142

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Pulmonary function testing in patients with pulmonary arterial hypertension

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Received 22 November 2008; accepted 2 March 2009
Available online 28 April 2009

KEYWORDS
Airway obstruction;
Pulmonary arterial hypertension;
Pulmonary function test;
Pulmonary diffusion capacity

Summary
Background: Although previous studies have shown that peripheral airway obstruction can occur in idiopathic PAH (IPAH), pulmonary function tests have not been well-studied in patients with PAH associated with congenital heart disease (CHD-PAH) and connective tissue disease (CTD-PAH).
Methods: A multicenter prospective study was performed in PAH patients in China. Pulmonary function tests were evaluated in 190 PAH patients.
Results: Total lung capacity (TLC), residual volume (RV) and total airway resistance (Rtot) were similar in PAH patients and controls. However, measures of airflow, including vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC and MEF_{50} were decreased in PAH group. Single-breath diffusion capacity for carbon monoxide (DL_{CO}) was also decreased in PAH patients. Expiratory flow–volume curves showed reduction and a curvilinear appearance in patients with PAH. Similar changes were observed among the various subgroups of IPAH, CHD-PAH, and CTD-PAH patients. More CTD-PAH patients had abnormal DL_{CO}.
Conclusions: Airway obstruction is common in IPAH, CHD-PAH and CTD-PAH patients. CTD-PAH patients have lower DL_{CO}. Hemodynamics, serum markers and exercise capacity parameters did not correlate well with pulmonary function indices.

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doi:10.1016/j.rmed.2009.03.009

Introduction

Pulmonary arterial hypertension (PAH) is a condition characterized by pulmonary vascular growth and proliferation, leading to increased pulmonary vascular resistance and right heart dysfunction.[1] Previous studies have shown that idiopathic PAH (IPAH), and PAH occurring in association with congenital heart disease (CHD-PAH) and connective tissue disease (CTD-PAH) have similar pathologies such as medial hypertrophy of muscular and elastic arteries, dilation and intimal atheromas of elastic pulmonary arteries and right ventricular hypertrophy.[2] In addition, Giaid et al studied the distribution of endothelin-1 in lung specimens in pulmonary hypertension patients and found IPAH, CHD-PAH and CTD-PAH are all associated with the increased expression of endothelin-1 in vascular endothelial cells, suggesting that the production of endothelin-1 may contribute to pulmonary hypertension.[3] Considering the proximity of pulmonary vasculature and peripheral airways, it is possible that the latter may be affected either by mechanical encroachment of enlarged vessels or by mediators of increased smooth muscle tone or proliferation.[4]

Because peripheral airways affected follow the pulmonary vasculature, it is reasonable to postulate that pulmonary function might be affected by the development of pulmonary hypertension. However, previous studies of pulmonary function in primary pulmonary hypertension (PPH) (or IPAH) have been contradictory, with normal lung volumes, restrictive ventilatory pattern, and airway obstruction.[5–7] In a German study of PPH, peripheral airway obstruction was common, but that study did not include CHD-PAH and CTD-PAH.[7] Pulmonary function tests have not been well-studied in patients with CHD-PAH and CTD-PAH and the mechanism of changes in pulmonary function remains unclear.

This cross sectional study was designed to identify pulmonary function characteristics in different forms of PAH, including IPAH, CHD-PAH and CTD-PAH, and to explore the relationship among pulmonary function parameters, hemodynamic parameters, serum markers and exercise capacity.

Patients and methods

Patients

This is a multicenter prospective study assessing pulmonary function indices in IPAH, CHD-PAH, and CTD-PAH from June 2006 to February 2008. The study protocol was reviewed and approved by Shanghai Pulmonary Hospital's ethics committee. Informed consent was obtained from all individuals.

Patients with PAH were distributed into three diagnostic groups using the Venice classification criteria: (a) idiopathic, no etiologic agent identified; (b) congenital heart disease diagnosed by way of hemodynamic assessment and echocardiography; and (c) connective tissue disease in accordance with conventional clinical criteria.[8]

One hundred and ninety patients with PAH were enrolled in this study. Only patients who had undergone pulmonary function tests and cardiac catheterization within 30 days were included. None of the patients had a history of lung disease, such as chronic obstructive or interstitial lung disease, lung cancer, or extensive tuberculosis. Fifty-six non-smoking adult volunteers without pulmonary or cardiac dysfunction and matched for age and sex were enrolled as control group to compare with patients with PAH. Pulmonary function indices were also compared among three diagnostic subgroups of PAH.

According to WHO functional classification at enrollment, all PAH patients were divided into two groups: Class II and Class III/IV. Clinical manifestations, RHC and pulmonary function indices were compared between two groups.

Six-minute walk distance, pulmonary function test and hemodynamic measurements

Six-minute walk tests were performed in accordance with the American Thoracic Society guidelines.[9] Pulmonary function tests were carried out using Master Screen Diffusion (Erich Jaeger Inc., Germany) according to standard protocols.[10] Pulmonary function indices including lung volumes, flow/volume curves, single-breath diffusion capacity for carbon monoxide (corrected for haemoglobin levels) and total airway resistance were determined with the patients sitting upright and breathing through a flanged mouthpiece inside the lips. The results were expressed as percent of predicted (% pred).

Right heart catheterization was performed through Swan–Ganz catheter (Edwards Lifesciences World Trade Co., Ltd, USA) in all enrolled PAH patients according to standard procedures.[11] Baseline hemodynamic variables were measured including right atrial pressures, pulmonary arterial pressures, pulmonary capillary wedge pressures, and systemic pressures. Cardiac output (CO) was measured by the Fick's principle or themodilution method and cardiac index (CI) was calculated by CO divided body surface area. Pulmonary vascular resistance (PVR) was calculated using the standard formula and was expressed in Wood units.

Statistical analysis

SPSS 13.0 software was applied in data management (SPSS Inc, Chicago, Illinois). The data were expressed as mean $\pm$ SD or frequency and proportions. Differences between proportions were compared with a χ^2 test; differences between two groups were assessed by independent sample t test; differences among multiple groups were performed by ANOVA. Multivariate regression analysis was performed to determine the independent association of clinical variables with pulmonary function indices. Correlation coefficients among pulmonary function parameters, hemodynamic parameters, 6 MWD, and serum markers are expressed as Spearman correlation coefficients. A p value less than 0.05 was considered to be significant.

Results

Baseline characteristics of study population

The clinical characteristics of PAH patients and controls were summarized in Table 1. The PAH patients population

Table 1 Clinical characteristics of controls and all PAH patients.

	Control	All PAH
Total number (*n*)	56	190
Sex (male/female)	21/35	50/140
Age (years)	34.80 ± 10.02	31.78 ± 11.28
Height (cm)	162.66 ± 8.40	162.52 ± 7.65
Weight (kg)	58.96 ± 14.12	55.17 ± 11.69

did not differ from the controls in age, sex, height and weight ($p > 0.05$). Five male patients (2 IPAH, 3 CHD-PAH) had a smoking history before onset, and all have quit smoking after onset of breathless. No female patients had smoking history.

Pulmonary function test comparison between controls and PAH patients

Compared with controls, lung volumes were normal in all patients. Total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC) and total airway resistance (Rtot) in PAH patients were close to controls and predicted values (Table 2).

Inspiratory vital capacity (VC), forced inspiratory vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and the ratio of FEV_1/FVC were reduced compared with controls (Table 2). The mean expiratory flow rates at 50% (MEF_{50}) were 79.96 ± 20.72% predicted in controls and 55.18 ± 23.80% predicted in PAH patients. Furthermore, the flow–volume curves indicated considerable peripheral airflow obstruction in PAH patients (Fig. 1). All these results showed that there was moderate peripheral airway obstruction in PAH patients.

The single-breath diffusion capacity for carbon monoxide (DL_{CO}) in PAH patients was 65.59 ± 19.64% predicted, which was significantly decreased compared with that of controls (85.32 ± 19.37% predicted).

Baseline characteristics comparison among IPAH, CHD-PAH and CTD-PAH patients

At right heart catheterization, all PAH patients showed moderate-to-severe pulmonary hypertension and pulmonary capillary wedge pressure was normal. Patients with PAH were classified according to different etiologies. Mean age was 34.98 ± 11.39 years in IPAH, 28.66 ± 10.80 years in CHD-PAH and 34.07 ± 10.43 years in CTD-PAH. The male/female ratio among each PAH group was similar. The height and weight were similar among different PAH groups. The ratio of WHO functional Class II and III–IV was similar among the three groups, and 6-min walk distance showed no significant difference among three PAH groups. The serum markers such as uric acid (UA) were similar among the three PAH groups. Brain natriuretic peptide (BNP) and endothelin-1 (ET-1) in CHD-PAH group were lower than those in IPAH group and CTD-PAH group. SaO_2 (arterial oxygen saturation) and SvO_2 (mixed venous oxygen saturation) were similar between IPAH and CTD-PAH. But SaO_2 was lower and SvO_2 was higher in CHD-PAH than other two groups, this may be caused by left-to-right or right-to-left intracardiac shunting in CHD-PAH (see Table 3).

The results of hemodynamic assessment are shown in Table 3. Mean pulmonary artery pressure (PAP) in the CHD-PAH group was 75.08 ± 20.75 mm Hg, which was significantly higher than that in the IPAH group (59.90 ± 17.07 mm Hg; $p < 0.001$) and the CTD-PAH group (54.92 ± 15.80 mm Hg; $p < 0.001$); CI in CHD-PAH group was 3.22 ± 1.29 l/min/m^2 and significantly higher than 2.50 ± 0.99 l/min/m^2 in the IPAH group ($p < 0.001$) and 2.50 ± 0.93 l/min/m^2 in the CTD-PAH group ($p < 0.001$); the RAP and PVR among the three groups showed no statistical difference.

Pulmonary function indices comparison among IPAH, CHD-PAH and CTD-PAH patients

The indices of pulmonary function test in different etiologies of PAH were also compared. After adjustment for age and sex, mPAP, CI, BNP, and ET-1 level, lung volumes such

Table 2 The comparison of pulmonary function indices in patients with all PAH patients and controls.

	All PAH ($n = 190$)	Control ($n = 56$)	Mean difference (95% CI)	*p*-Value
TLC (% predicted)	88.46 ± 12.15	91.98 ± 11.26	3.52 (−0.08 to 7.12)	0.06
VC (% predicted)	82.57 ± 14.58	93.23 ± 13.70	10.68 (2.12–6.36)	<0.001
FVC (% predicted)	83.86 ± 14.80	95.63 ± 14.16	11.76 (7.38–16.15)	<0.001
FEV_1 (% predicted)	78.08 ± 15.86	91.29 ± 17.20	13.21 (8.36–18.05)	<0.001
FEV_1/FVC (% predicted)	95.30 ± 11.00	99.88 ± 8.83	4.57 (1.75–7.40)	0.002
RV (% predicted)	96.85 ± 19.41	92.89 ± 21.70	−3.96 (−10.37 to 2.46)	0.22
MEF_{50} (% predicted)	55.18 ± 23.80	79.96 ± 20.72	24.78 (17.85–31.72)	<0.001
FRC (% predicted)	92.22 ± 15.70	94.93 ± 20.39	2.71 (−2.35 to 7.77)	0.29
Rtot (% predicted)	112.85 ± 24.09	111.08 ± 16.05	−1.76 (−8.15 to 4.62)	0.58
DL_{CO} (% predicted)	65.74 ± 19.86	85.32 ± 19.37	19.58 (13.67–25.50)	<0.001
FVC/DL_{CO}	1.37 ± 0.41	1.18 ± 0.32	0.19 (0.09–0.29)	<0.001

TLC, total lung capacity; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; RV, residual volume; FRC, functional residual capacity; MEF50, maximal expiratory flow 50% of exhaled VC; Rtot, airway resistance; DL_{CO}, single-breath diffusion capacity for carbon monoxide (corrected for haemoglobin levels). Values are expressed as mean ± SD and percentage of measured to predicted values (% pred).

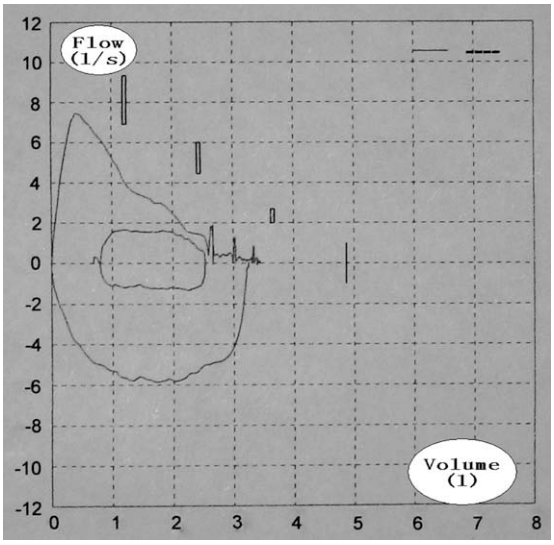

Figure 1 Flow—volume curve of a 25-year-old non-smoking man with idiopathic pulmonary arterial hypertension (IPAH). Predicted values (bar) for individual forced vital capacity are also shown.

as TLC, FEV_1/FVC, and Rtot were similar in the three PAH groups (Table 4).

Compared with the IPAH group, VC, FVC, FEV_1 and MEF_{50} were decreased in the CHD-PAH group. RV and FRC were slightly decreased in the CTD-PAH compared with IPAH and CHD-PAH, indicating that mild restrictive abnormalities exist in the CTD-PAH group. All three groups demonstrated decreased DL_{CO}. Compared with IPAH and CHD-PAH, the CTD-PAH group showed the greatest abnormality in DL_{CO}.

Pulmonary function comparison between WHO-FC II, and III—IV

There were no significant differences in TLC, VC, FVC, FEV_1, FEV_1/FVC, RV, MEF_{50} and Rtot between the WHO-FC II group and III—IV group (see Table 5). Only DL_{CO} in WHO-FC III—IV group was significantly decreased compared with WHO-FC II (61.11 ± 18.86 vs. 71.46 ± 19.68% predicted, $p < 0.001$).

If grouped by mean right atrial pressure, mean pulmonary arterial pressure and mean interval time from onset of symptoms to diagnosis, there were no differences in pulmonary function indices (data not shown).

Correlations of pulmonary function indices with hemodynamics, serum markers and exercise capacity

Correlations of selected pulmonary function indices among hemodynamics, serum markers and exercise capacity were shown in Table 6. No pulmonary function indices correlated well with hemodynamics or serum markers or exercise capacity findings.

The FEV_1 had a mild and moderate correlation, with ET-1 of -0.24, and with 6MWD of 0.20 (Fig. 2). CI had a moderate correlation with DL_{CO} ($r = 0.24$). DL_{CO} had a positive correlation with 6-min walk distance and a negative correlation with ET-1, the correlation coefficient was 0.27 and -0.24, respectively.

Discussion

This study confirms previous studies suggesting that peripheral airway obstruction occurs in IPAH.[7,12,13] Our study

Table 3 Clinical characteristics of different PAH patients.

	IPAH	CHD-PAH	CTD-PAH
Total number (*n*)	62	91	37
Sex (male/female)	18/44	25/66	7/30
Age (years)	34.98 ± 11.39	28.66 ± 10.80**	34.07 ± 10.43#
Height (m)	163.71 ± 8.09	161.65 ± 7.52	162.65 ± 7.10
Weight (kg)	59.44 ± 12.83	51.40 ± 9.29	57.27 ± 12.29
WHO-FC (II/III—IV)	26/36	47/44	13/24
Six-min walk distance (m)	417.34 ± 94.41	426.26 ± 98.59	381.25 ± 114.25
Hemodynamics			
RAP (mm Hg)	5.62 ± 4.89	5.14 ± 3.88	5.59 ± 4.98
mPAP (mm Hg)	59.90 ± 17.07	75.08 ± 20.75**	54.92 ± 15.80##
PVR (Wood Units)	15.65 ± 8.13	16.59 ± 8.83	13.06 ± 7.65
CI ($l/min/m^2$)	2.50 ± 0.99	3.22 ± 1.29**	2.50 ± 0.93##
UA (μmol/l)	360.07 ± 104.50	353.98 ± 111.19	347.98 ± 115.79
BNP (fmol/ml)	1176.18 ± 984.63	773.72 ± 688.65*	1244.21 ± 1156.23#
ET-1 (fmol/ml)	0.91 ± 0.60	0.69 ± 0.49*	0.92 ± 0.55#
SaO_2 (%)	92.61 ± 6.28	86.79 ± 9.37**	92.67 ± 4.53##
SvO_2 (%)	63.77 ± 12.43	72.73 ± 10.22**	59.81 ± 12.06##

RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CI, cardiac index; WHO-FC, World Healthy Organization Functional Class; UA, uric acid; BNP, brain natriuretic peptide; ET-1, endothelin-1; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation. Other abbreviations are as in Table 2.
*$p < 0.05$, **$p < 0.01$ vs. IPAH group using one-way ANOVA or Chi-square test.
#$p < 0.05$, ##$p < 0.01$ vs. CHD-PAH group using one-way ANOVA or Chi-square test.

Table 4 The comparison of pulmonary function indices in patients with IPAH, CHD-PAH and CTD-PAH.

	IPAH ($n = 62$)	CHD-PAH ($n = 91$)	CTD-PAH ($n = 37$)
TLC (% predicted)	90.71 ± 1.65	88.26 ± 1.46	84.68 ± 2.15
VC (% predicted)	86.91 ± 1.91	80.16 ± 1.70*	80.43 ± 2.47
FVC (% predicted)	88.86 ± 1.91	81.58 ± 1.70*	80.30 ± 2.47*
FEV_1 (% predicted)	83.09 ± 2.05	74.15 ± 1.82**	76.83 ± 2.65*
FEV_1/FVC (% predicted)	97.09 ± 1.39	92.76 ± 1.23	97.78 ± 1.78
RV (% predicted)	100.18 ± 2.34	99.19 ± 2.06	84.55 ± 2.99**##
MEF_{50} (% predicted)	61.50 ± 2.91	50.06 ± 2.59*	57.60 ± 3.76
FRC (% predicted)	94.48 ± 1.95	93.62 ± 1.72	83.48 ± 2.49**##
Rtot (% predicted)	108.62 ± 3.27	114.00 ± 2.85	116.64 ± 4.14
DL_{CO} (% predicted)	62.92 ± 2.47	71.21 ± 2.20	56.35 ± 3.20##
FVC/DL_{CO}	1.52 ± 0.45	1.20 ± 0.31**	1.53 ± 0.41##

Abbreviations are as in Table 2.
*$p < 0.05$, **$p < 0.01$ vs. IPAH group using one-way ANOVA.
#$p < 0.05$, ##$p < 0.01$, vs. CHD-PAH group using one-way ANOVA.
Multivariate analysis controlling for age, sex, mPAP, CI, BNP, and ET-1.

also showed that peripheral airway obstruction occurs in CHD-PAH and CTD-PAH. Peripheral airflow obstruction was indicated by reduction in the MEF_{50} to 55.18 ± 23.80 predicted. After being divided by different etiologies, the most serious obstructive abnormality was observed in CHD-PAH, then CTD-PAH, and lastly IPAH. CTD-PAH also showed mild restrictive abnormalities. Following worsening WHO function class, DL_{CO} decreased sharply. There was no more than moderate correlation between pulmonary function indices and serum or hemodynamic parameters.

Peripheral airway obstruction is common in PAH patients. Our study confirmed that peripheral airway obstruction is the most striking characteristics of pulmonary function test in IPAH, CHD-PAH and CTD-PAH patients; MEF_{50} may be the best index to describe the severity of obstruction. These findings are in agreement with the study of Meyer. Their study showed that in PPH patients, TLC was almost normal, RV increased and VC decreased.[7] Our study showed that not only IPAH but also CHD-PAH and CTD-PAH showed peripheral airway obstruction. However, we could not confirm that peripheral airway obstruction was more pronounced in severe disease as described in Meyer's study.

The earliest change associated with peripheral airway obstruction is thought to be a slow-down in the terminal portion of the spirogram, even when the initial part of the spirogram is barely affected.[14] This slow-down of expiratory flow is most obviously reflected in a concave shape of the flow—volume curve. Quantitatively, it is reflected in a proportionally greater reduction in the instantaneous flow measured at 50% of the FVC exhaled than in FEV_1. MEF_{50} has been used by many authors as a sensitive index of peripheral airflow limitation in chronic obstructive pulmonary disease, in occupational lung disease or in primary pulmonary hypertension.[12,15,16] In our study, MEF_{50} was significantly decreased in all PAH groups as compared to the control group. Compared among different etiologies of PAH, MEF_{50} was 59.52 ± 24.27% predicted in IPAH, 48.89 ± 27.45% predicted in CHD-PAH and 59.95 ± 33.92% predicted in CTD-PAH indicating that peripheral airway obstruction is common in IPAH, CHD-PAH and CTD-PAH.

Considering all PAH patients, the airway resistance as a whole did not differ significantly from healthy controls. This is plausible since airflow resistance is rarely used to identify airflow obstruction in clinical practice. It is more sensitive for detecting narrowed extrathoracic or large central intrathoracic airways than peripheral intrathoracic airways.[14] Data from asthmatics show that even major obstruction of peripheral airways can occur without recognized increases of airway resistance.[17]

Probable causes of peripheral airway obstruction

In most of our PAH patients, MEF_{50} was reduced compared with the control group. The underlying cause of peripheral airway obstruction in PAH is still unknown. In the early 1980s, some authors interpreted the finding of peripheral airflow obstruction as merely a result of the pathological changes in the pulmonary vasculature.[18] Although the true reason is still unclear, those studies may not fully explain the cause of peripheral airway obstruction in PAH. Researchers have begun to question whether abnormal endothelial function may play an important role in the cause of peripheral airway obstruction. Abnormalities in endothelial function, including impaired production of prostacyclin and nitric oxide and excessive synthesis of endothelin have well-known effects on

Table 5 The comparison of pulmonary function indices in patients with WHO-FC II, and III/IV.

	WHO-FC II ($n = 86$)	WHO-FC III—IV ($n = 104$)
TLC (% predicted)	89.52 ± 9.85	87.63 ± 13.67
VC (% predicted)	84.79 ± 14.33	80.77 ± 14.60
FVC (% predicted)	86.03 ± 14.04	82.11 ± 15.23
FEV_1 (% predicted)	79.95 ± 13.52	76.57 ± 17.44
FEV_1/FVC (% predicted)	95.52 ± 9.01	95.13 ± 12.41
RV (% predicted)	97.19 ± 21.25	96.58 ± 17.90
MEF_{50} (% predicted)	56.06 ± 23.38	54.46 ± 24.22
FRC (% predicted)	93.31 ± 15.51	91.34 ± 15.87
Rtot (% predicted)	114.74 ± 22.54	111.36 ± 25.25
DL_{CO} (% predicted)	71.46 ± 19.68	61.11 ± 18.86**

Abbreviations are as in Table 2.
**$p < 0.01$ vs. WHO-FC II group using Chi-square test.

Table 6 Correlation of pulmonary function indices with hemodynamics, serum markers and exercise capacity.

	VC %	DL_{CO} %	FEV_1 %	MEF_{50} %	FEV_1/FVC	FVC/DL_{CO}
mPAP	−0.07	0.13	−0.04	−0.02	0.004	−0.18*
PVR	−0.19*	−0.10	−0.19*	−0.15	−0.03	−0.03
CI	0.09	0.24**	0.13	0.12	0.04	−0.13
UA	−0.15*	−0.01	−0.06	0.01	0.02	−0.04
BNP	−0.23**	−0.09	−0.18*	−0.09	0.06	−0.05
ET-1	−0.29**	−0.24**	−0.24**	−0.15	0.006	0.07
6MWD	0.27**	0.27**	0.20**	0.08	0.01	−0.14

Abbreviations are as in Tables 2 and 3.
*$p < 0.05$; **$p < 0.01$.

the bronchial system.[19–21] Endothelin-1 mimics several features of asthma, including bronchospasm, airway remodelling, inflammatory cell recruitment and activation, edema, mucus secretion and airway dysfunction. ET-1 also possesses mitogenic effects on smooth muscle cells and fibroblasts and is a very potent bronchoconstrictor.[3,19] Thus, the observed peripheral obstruction may be a result of some spill over of endothelin from the vasculature into the airway system. A recent study, examining the effect of the endothelin receptor antagonist bosentan on endothelin-induced bronchoconstriction, showed that bosentan completely prevented ET-receptor agonist (IRL1620) induced bronchoconstriction.[22] Spiekerkoetter et al. found that inhaled salbutamol has beneficial acute effects on pulmonary function, blood gases and hemodynamics in patients with primary pulmonary hypertension.[12] Their studies may be helpful in understanding the mechanism of peripheral airway obstruction in PAH, and may suggest another therapeutic target in patients with PAH.

Probable causes of reduction in DL_{CO}

In our study, hemodynamics, serum markers and exercise capacity parameters did not correlate well with DL_{CO} and other pulmonary function indices. The mechanism underlying decreased DL_{CO} in PAH remains to be elucidated. DL_{CO} has been primarily considered a marker of capillary surface area. Studies support the concept that reduced DL_{CO} in IPAH, CHD-PAH and CTD-PAH can be explained by the increase in alveolar capillary membrane thickness, which may caused by the proliferation of endothelial cells.[23] The reduction of perfused pulmonary capillary bed may fit the pathological findings described at the Third World Symposium on Pulmonary Artery Hypertension: all forms of pulmonary hypertension have some common pathologic features regardless of their etiologies, that is to say, medial hypertrophy of muscular and elastic arteries, dilation and intimal atheromas of elastic pulmonary arteries.[24]

Clinical implications

The negative correlations of the FEV_1 and DL_{CO} with ET-1 are difficult to explain. Previous studies have shown that ET-1 is an important factor involved in the pathogenesis of PAH. Further investigation is needed to determine whether ET-1 is involved in the pathogenesis of airway abnormalities. DL_{CO} has positive correlation with 6-min walk distance. Our results concur with Sun's study,[25] which found a proportional reduction in DL_{CO} supporting the finings that the primary pathological process involves the blood vessels of the lungs. But we did not agree with

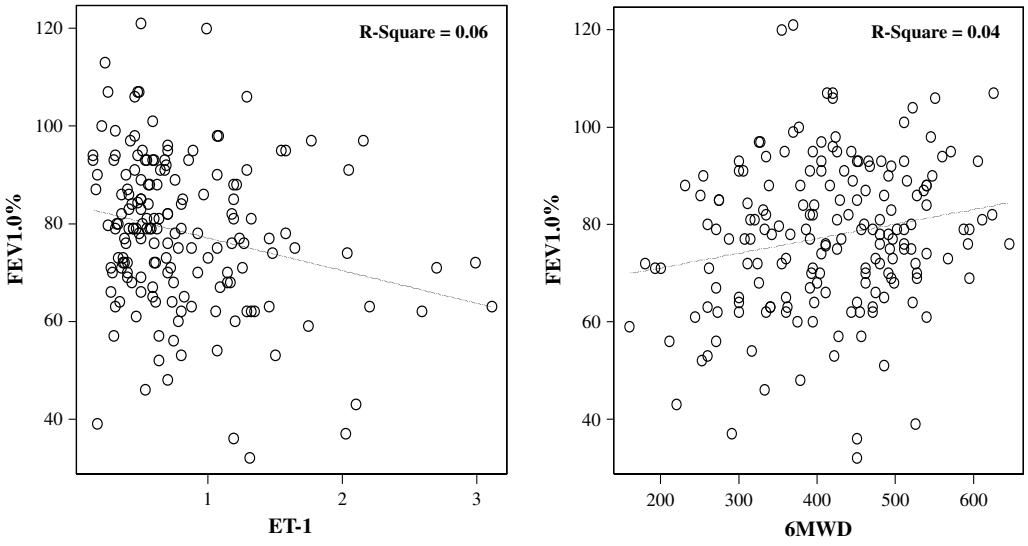

Figure 2 Relationship between FEV1 and ET-1. A moderate negative correlation is seen ($r^2 = 0.06$, left figure); relationship between FEV1 and 6MWD. A moderate positive correlation is seen ($r^2 = 0.04$, right figure).

Steenhuis's study, which showed that an increased pulmonary vascular resistance was associated with a decrease in pulmonary membrane diffusion capacity.[26] Previous evidence suggests that PAH is strongly associated with a FVC/DL_{CO} (% predicted) ratio of greater than 1.4,[27] but in our study the correlation coefficient of mPAP with FVC/DL_{CO} was only −0.18. Further studies are needed to explain the difference.

In conclusion, the notable characteristics of pulmonary function tests in PAH were peripheral airway obstruction and reduced diffusing capacity for carbon monoxide. MEF_{50} may be the most important measurement to evaluate peripheral airway obstruction in pulmonary arterial hypertension. No hemodynamic measurements, serum markers or exercise capacity parameters correlated well with pulmonary function indices. Pulmonary function testing has limited value to predict hemodynamics in pulmonary arterial hypertension and limited value in diagnosis of IPAH, CHD-PAH and CTD-PAH. These findings suggest that further studies are indicated.

Conflict of interest

All authors have no conflicts of interest to disclose.

Funding resource

The study was supported by China National 973 Project (2007CB512008).

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