

## ORIGINAL ARTICLE

## Peripheral airway obstruction in primary pulmonary hypertension

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Thorax 2002;57:473-476

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Revised version received  
3 December 2001  
Accepted for publication  
13 December 2001

**Background:** As there is controversy about changes in lung function in primary pulmonary hypertension (PPH), lung mechanics were assessed with a focus on expiratory airflow in relation to pulmonary haemodynamics.

**Methods:** A cross sectional study was performed in 64 controls and 171 patients with PPH (117 women) of mean (SD) age 45 (13) years, pulmonary artery pressure (PAPmean) 57 (15) mm Hg, and pulmonary vascular resistance 1371 (644) dyne.s/cm<sup>5</sup>.

**Results:** Mean (SD) total lung capacity was similar in patients with PPH and controls (98 (12)% predicted v 102 (17)% predicted, mean difference -4 (95% confidence interval (CI) -7.89 to -0.11); residual volume (RV) was increased (118 (24)% predicted v 109 (27)% predicted, mean difference 9 (95% CI 1.86 to 16.14); and vital capacity (VC) was decreased (91 (16)% predicted v 102 (10)% predicted, mean difference -11 (95% CI 15.19 to -6.80). RV/TLC was increased (117 (27)% predicted v 97 (29)% predicted, mean difference 20 (95% CI 12.3 to 27.8)) and correlated with PAPmean ( $r=0.31$ ,  $p<0.001$ ). In patients with PAPmean above the median of 56 mm Hg, RV/TLC was further increased (125 (32)% predicted v 111 (22)% predicted, mean difference -14 (95% CI -22.2 to -5.8)). Expiratory flow-volume curves were reduced and curvilinear in patients with PPH.

**Conclusions:** Peripheral airway obstruction is common in PPH and is more pronounced in severe disease. This may contribute to symptoms. Reversibility of bronchodilation and relation to exercise capacity need further evaluation.

Primary pulmonary hypertension (PPH) is a rare and del-  
eterious pulmonary vascular disease of unknown origin.<sup>1</sup>  
The functional limitations of patients with PPH are  
mainly caused by progressive right heart failure and impaired  
pulmonary gas exchange. It is, however, unclear whether PPH  
may also be associated with changes in lung mechanics.

Considering the proximity of the pulmonary vasculature  
and the peripheral airways, it is possible that the latter may be  
affected either by mechanical encroachment of dilated vessels  
or by mediators of increased smooth muscle tone or  
proliferation.<sup>1,2</sup> Experimental models of pulmonary hyper-  
tension induced by chronic hypoxia or monocrotaline indicate  
that structural changes in the pulmonary vasculature also  
extend to the airways, resulting in increased airways  
resistance.<sup>3,4</sup> In humans, however, data on pulmonary  
function in PPH reported in small series of patients or case  
reports have been contradictory, with normal lung volumes,<sup>5</sup> a  
restrictive ventilatory pattern,<sup>6-8</sup> and airway obstruction<sup>9-11</sup>  
being reported. In the national PPH registry in the USA a mild  
restrictive defect was found but no data on airflow were  
included.<sup>12</sup>

A cross sectional study was therefore designed to assess  
respiratory mechanics in a large well characterised European  
cohort of PPH patients recruited by the German PPH Study  
Group.<sup>11,13,14</sup> Expiratory airflow limitation and premature  
airway closure were found to be common in patients with PPH  
compared with reference values and controls.

## METHODS

One hundred and seventy one patients (117 women) with  
PPH<sup>15</sup> were enrolled at eight centres after written informed  
consent was obtained and approval by the local ethics  
committees. Four patients were active smokers and 12 had  
smoked in the past. None of the patients was on broncho-  
dilator treatment or had a history or signs of lung disease

(chronic obstructive or interstitial lung disease, lung cancer,  
extensive tuberculosis). In 32% of the patients PPH treatment  
included iloprost inhalation. Patients with clinical or radio-  
logical signs of cardiopulmonary decompensation were not  
included. Since reported reference values for expiratory flow  
may vary substantially,<sup>16</sup> 64 non-smoking volunteers without  
pulmonary or cardiac dysfunction and matched for age and  
sex were included.

## Lung function testing and haemodynamic measurements

Spirometric tests and body plethysmography (Erich Jaeger,  
MasterLabPro 4.2, Wuerzburg, Germany) were performed  
according to standard protocols.<sup>17</sup> Lung function reference  
values corrected for sex, age, and height were used.<sup>17</sup> Right  
heart catheterisation at rest was performed during the week  
before or after lung function testing, including measurement  
of cardiac output (CO) by the thermodilution method or the  
Fick principle.<sup>18</sup>

## Statistical analysis

The data are presented as mean (SD) values. Data analysis  
consisted of the two tailed Student's *t* test, the two sample  
proportion test, or linear regression analysis using the least  
squares method.<sup>19</sup> For subgroup analysis a split around the  
median value was used. A *p* value of <0.05 was considered  
significant.

## RESULTS

The patient population did not differ significantly from the  
controls in sex (68% v 60% women), age (45 (13) v 46 (13)  
years), height (167 (10) v 170 (8) cm), or body weight (68 (14)  
v 71 (13) kg). Patients with PPH were classified according to  
the New York Heart Association (NYHA) functional classes II  
(23% of patients), III (61%), and IV (16%), mean 2.9 (0.6).

**Table 1** Mean (SD) values of lung function indices in 171 patients with PPH and 64 controls

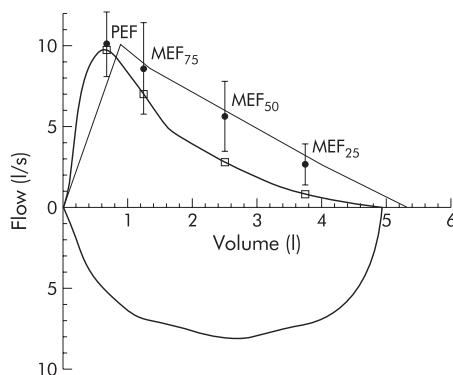
	PPH (n=171)	Controls (n=64)	Mean difference (95% CI)	p value*
TLC (% predicted)	98 (12)	102 (17)	-4 (-7.9 to -0.1)	0.046
RV (% predicted)	118 (24)	109 (27)	9 (1.9 to 16.1)	<0.001
RV/TLC (% predicted)	117 (27)	97 (29)	20 (12.3 to 27.8)	<0.001
Rtot (% of upper limit)	98 (42)	91 (42)	7 (-5.1 to 19.1)	0.26
VC (% predicted)	91 (16)	102 (10)	-11 (15.2 to -6.8)	<0.001
FEV <sub>1</sub> (% predicted)	83 (15)	106 (9)	-23 (-26.9 to -19.1)	<0.001
FEV <sub>1</sub> /VC (%)	76 (8)	84 (5)	-8 (10.09 to -5.90)	<0.001
PEF (% predicted)	85 (21)	98 (12)	-13 (-18.5 to -7.6)	<0.001
MEF <sub>75</sub> (% predicted)	82 (24)	103 (13)	-21 (-27.2 to -14.8)	<0.001
MEF <sub>50</sub> (% predicted)	66 (24)	101 (19)	-35 (-41.5 to -28.5)	<0.001
MEF <sub>25</sub> (% predicted)	46 (23)	82 (22)	-36 (-42.5 to -29.5)	<0.001

CI = confidence interval; TLC = total lung capacity; RV = residual volume; Rtot = airway resistance; VC = vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 second; PEF = peak expiratory flow; MEF<sub>75</sub>, MEF<sub>50</sub>, MEF<sub>25</sub> = maximal expiratory flow at 25%, 50%, and 75% of exhaled VC, respectively. \*Student's *t* test.

In PPH patients the mean pulmonary artery pressure (PAP-mean) was increased to 57 (15) mm Hg (range 27–134), CO was reduced to 3.3 (1.2) l/min (range 1.4–8.2), and central venous pressure (CVP) was increased to 8 (5) mm Hg. The pulmonary capillary wedge pressure (PCWP) obtained in 151 patients was normal (7 (3) mm Hg) and the pulmonary vascular resistance (PVR) was increased to 1371 (644) dyne.s/cm<sup>5</sup> (range 308–4250).

Total lung capacity (TLC) in patients with PPH (5.5 (1.2) l) was close to reference values and to controls (table 1). However, inspiratory vital capacity (VC, 3.4 (0.9) l) and forced expiratory volume in 1 second (FEV<sub>1</sub>, 2.5 (0.7) l) were reduced compared with predicted values and controls. Thus, there was moderate lung hyperinflation in PPH as indicated by an increase in residual volume (RV) and in the RV/TLC ratio (table 1). In control subjects TLC (6.0 (1.0) l), VC (4.0 (0.8) l), and FEV<sub>1</sub> (3.4 (0.7) l) were close to reference values (table 1).

In patients with PPH there were weak but significant linear correlations between the RV/TLC ratio, an index of lung hyperinflation, and the following parameters of airway obstruction: total airway resistance (Rtot;  $r=0.24$ ;  $p=0.002$ ), FEV<sub>1</sub>/VC ( $r=0.22$ ;  $p=0.002$ ), maximal expiratory flows at 50% and 75% of exhaled VC (MEF<sub>50</sub>;  $r=0.43$ ,  $p<0.001$ ; MEF<sub>25</sub>;  $r=0.32$ ,  $p<0.001$ ). For the PPH patients as a whole, Rtot did not differ significantly from reference values or from controls (table 1). However, increased Rtot values were found in a substantial proportion of patients with PPH with values of  $>0.36$  kPa.s/l ( $>120\%$  of reference value) in 49 patients (29%) and six controls (9%;  $p<0.001$ , two sample proportion test) and  $>0.45$  kPa.s/l ( $>150\%$ ) in 23 patients (14%) and in none of the controls ( $p<0.001$ ).



**Figure 1** Flow-volume curve of a 27 year old non-smoking man with primary pulmonary hypertension (PPH, bold line). Predicted values (thin line) and predicted values corrected for individual vital capacity (dots  $\pm$  SD) are also shown.

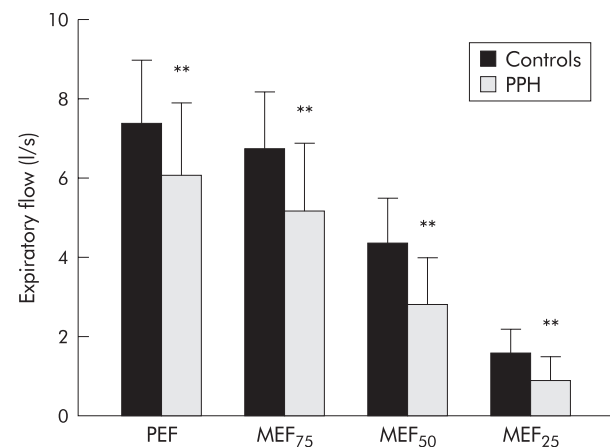
The FEV<sub>1</sub>/VC ratio in patients with PPH was significantly reduced compared with controls (table 1). Moreover, the prevalence of airway obstruction with an FEV<sub>1</sub>/VC ratio of  $<70\%$  or  $<60\%$  was significantly increased in patients with PPH ( $<70\%$  in 37 patients (22%) and no controls,  $p<0.01$ ;  $<60\%$  in 10 patients and no controls,  $p<0.01$ ).

A representative example of the expiratory flow-volume curves with an abnormal curvilinear shape is shown in fig 1. Mean expiratory flow rates are shown in fig 2. A significant reduction in peak expiratory flow (PEF), MEF<sub>75</sub>, MEF<sub>50</sub>, and MEF<sub>25</sub> was seen compared with predicted values (table 1) and control subjects (fig 2).

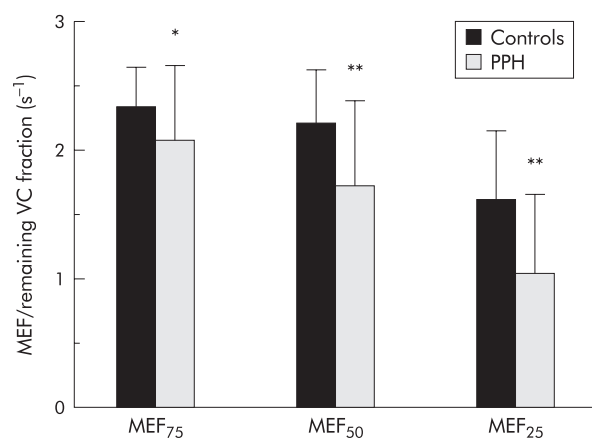
Airflow limitation was more pronounced at lower values of VC. MEF<sub>75</sub>, MEF<sub>50</sub>, and MEF<sub>25</sub> were reduced by 18%, 34%, and 54%, respectively, from predicted values and by 11%, 37%, and 44% compared with controls (fig 2).

To account for the decreased VC in patients with PPH, flow rates were also corrected for individual VC values. The ratio of expiratory flow rates and remaining fractions of VC showed a similar highly significant reduction during end expiration (fig 3).

When patients were divided according to median PAPmean, RV/TLC was significantly higher in patients with a PAPmean above the median, but expiratory airflow parameters, Rtot, and FEV<sub>1</sub> did not differ (table 2). Similarly, RV/TLC showed a weak linear correlation with PAPmean ( $r=0.31$ ;  $p<0.001$ ) whereas the other indices of lung function were independent of pulmonary haemodynamics (data not shown).



**Figure 2** Expiratory airflow in 171 patients with PPH and 64 controls. Expiratory airflow was significantly decreased in PPH. The reduction in airflow was most prominent during the lower part of vital capacity (MEF<sub>50</sub> and MEF<sub>25</sub>), indicating obstruction of peripheral airways in PPH. \*\* $p<0.01$  v controls (Student's *t* test).



**Figure 3** To correct for differences in vital capacity (VC), a ratio of MEF<sub>75</sub>, MEF<sub>50</sub> and MEF<sub>25</sub> and the respective fraction of remaining VC, e.g. MEF<sub>75</sub> × (0.75 × VC)<sup>-1</sup> was calculated for 171 PPH patients and 64 controls. The progressive reduction in MEF during end expiration was independent of the reduced VC in patients with PPH. \*p=0.04 and \*\*p<0.001 v controls (Student's *t* test).

Since smoking may affect small airways function, the 16 patients with PPH who had a smoking history were analysed separately. In this subgroup the results of right heart catheterisation, spirometric testing, and body plethysmography did not differ from the total patient population except for a reduction in RV/TLC (100 (31)% predicted, p=0.02 v total group) and MEF<sub>25</sub> (33% predicted; p=0.03).

## DISCUSSION

The main finding of this study was significant peripheral airway obstruction in patients with PPH as indicated by end expiratory airflow limitation and premature airway closure leading to a reduction in VC.

Previous studies, including the US PPH registry, failed to demonstrate airway obstruction in patients with PPH.<sup>5, 12, 20</sup> Similarly, the frequently used criteria for airway obstruction (FEV<sub>1</sub>/VC <70%, Rtot >0.3 kPa.s/l) were not met by our patient group as a whole. However, the FEV<sub>1</sub>/VC ratio was significantly reduced in the patients with PPH compared with the controls. Moreover, the proportion of patients with an FEV<sub>1</sub>/VC

ratio of <70% or <60% together with increased Rtot was significantly higher than in the control group. These findings indicate airway obstruction in PPH.

Since subtle changes in the airway characteristics may be missed by using only the FEV<sub>1</sub>/VC ratio or Rtot,<sup>9</sup> flow-volume curves were used to analyse expiratory flow rates. Expiratory airflow was markedly decreased in patients with PPH, particularly during the effort independent end expiratory portion of the flow-volume curve obtained at lower values of VC. This resulted in a curvilinear curve, indicating peripheral airway obstruction, whereas the expiratory flow-volume loop is linearly reduced throughout expiration in a purely restrictive pattern of ventilation.<sup>21</sup> Moreover, although VC was mildly reduced in patients with PPH, the reduction in end expiratory flow remained significant after correction for VC. These findings are in agreement with previous observations in small groups of PPH patients.<sup>9, 10</sup> The indices of premature airway closure (RV and RV/TLC) were significantly increased in PPH, as reported earlier.<sup>9</sup> Our data show a significant correlation of expiratory airflow limitation with premature airway closure in PPH. With TLC remaining unchanged, the increase in RV encroaches on VC, resulting in VC reduction. In patients with chronic congestive heart failure (CHF) due to ischaemic or dilated cardiomyopathy we have found a similar reduction in VC, but without an increase in RV and obstruction.<sup>22, 23</sup> While in CHF cardiac enlargement may contribute to a reduction in VC, in PPH small airway obstruction predominantly affects VC by premature airway closure and lung hyperinflation.

There was no correlation between expiratory airflows and haemodynamic parameters in our patients, and MEF<sub>75</sub>, MEF<sub>50</sub> and MEF<sub>25</sub> did not differ between patients with a PAPmean above and below the median. These findings suggest that airflow limitation may occur independently of the severity of PPH. However, as RV/TLC was correlated with PAPmean, peripheral airflow obstruction may reflect the underlying vascular disease and its haemodynamic consequences. This concept is supported by experimental data<sup>3, 4</sup> and by a small study<sup>9</sup> in 11 patients with PPH showing that airflow limitation at the lower part of VC was associated with airway narrowing, bronchial wall thickening, and lymphocyte infiltrates.

It might be speculated that the increased production of cytokines and growth mediators in the pulmonary vasculature in PPH also causes proliferation in adjacent small airways.<sup>1</sup> Moreover, in PPH there is decreased endothelial synthesis of the vasodilator nitric oxide (NO)<sup>24</sup> and increased levels of the vasoconstrictor endothelin-1 (ET-1)<sup>25</sup> which might also affect

**Table 2** Mean (SD) lung function and haemodynamic indices in 171 patients with PPH subdivided into groups according to median mean pulmonary artery pressure (PAPmean)

	PAPmean ≤56 mm Hg (n=86)	PAPmean >56 mm Hg (n=85)	Mean difference (95% CI)	p value*
PAPmean (mm Hg)	47 (7)	68 (12)	-21 (-23.9 to -18.1)	<0.001
CVP (mm Hg)	6 (4)	10 (5)	-4 (-5.4 to -2.6)	<0.001
PCWP (mm Hg)	7 (3)	8 (3)	-1 (-1.9 to -0.1)	0.048
PVR (dyne.s/cm <sup>5</sup> )	1029 (431)	1784 (667)	-755 (-923.1 to -586.9)	<0.001
Cardiac output (l/min)	3.6 (1.1)	3.1 (1.2)	-0.5 (0.2 to 0.9)	0.026
TLC (% predicted)	99 (18)	96 (13)	3 (-1.7 to 7.7)	0.2
RV (% predicted)	113 (33)	122 (32)	-9 (-18.8 to 0.8)	0.07
RV/TLC (% predicted)	111 (22)	125 (32)	-14 (-22.2 to -5.8)	0.006
Rtot (% of upper limit)	95 (46)	101 (39)	-6 (-18.8 to 6.8)	0.26
VC (% predicted)	94 (15)	87 (15)	7 (2.5 to 11.5)	<0.001
FEV <sub>1</sub> (% predicted)	87 (15)	80 (16)	7 (2.4 to 11.7)	0.006
FEV <sub>1</sub> /VC (%)	75 (8)	77 (10)	-2 (-4.7 to 0.7)	0.2
PEF (% predicted)	88 (21)	81 (21)	7 (0.7 to 13.3)	0.045
MEF <sub>75</sub> (% predicted)	84 (23)	80 (24)	4 (-3.1 to 11.1)	0.37
MEF <sub>50</sub> (% predicted)	66 (23)	66 (26)	0 (7.4 to 7.4)	0.96
MEF <sub>25</sub> (% predicted)	46 (24)	46 (26)	0 (7.5 to 7.5)	0.98

CI = confidence interval; PAPmean = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = postcapillary wedge pressure; PVR = pulmonary vascular resistance; TLC = total lung capacity; RV = residual volume; Rtot = airway resistance; VC = vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 second; PEF = peak expiratory flow; MEF<sub>75, 50, 25</sub> = maximal expiratory flow at 25%, 50%, and 75% of exhaled VC, respectively. 7.5 mm Hg = 1 kPa. \*Student's *t* test.

peripheral airway function since both mediators have similar effects on vascular and airway smooth musculature.<sup>26, 27</sup> Coupling between pulmonary blood vessels and airways has been attributed to mechanical forces due to shared structural changes in vessels and airways, or to vascular rigidity leading to an impairment of lung elastic recoil.<sup>2</sup> It remains to be determined whether the presence of vasoconstrictive and proliferative mediators such as ET-1 or the lack of vasodilatory and antiproliferative mediators such as NO and prostacyclin may directly affect the function of peripheral airways in PPH.

In PPH the airway obstruction may be unidentified if only FEV<sub>1</sub>/VC or Rtot are measured, so measurement of expiratory flow is recommended during the routine evaluation of patients with PPH. Since expiratory airflow limitation may contribute to symptoms and exercise limitation in patients with PPH, pharmacological reversal of small airways dysfunction might be beneficial. Preliminary observations suggest reversibility of airway obstruction with salbutamol.<sup>28</sup> This observation is supported by a recent study in children with PPH and the Eisenmenger's syndrome in which inhalation of albuterol resulted in reversibility of airflow obstruction.<sup>29</sup> It also corresponds to data from patients with pulmonary hypertension secondary to CHF in whom the inhalation of ipratropium bromide improved FEV<sub>1</sub>, expiratory flow rates, and exercise limitation without affecting haemodynamics.<sup>30, 31</sup> Further evaluation of reversibility of peripheral airway obstruction and possible beneficial effects on exercise capacity and symptoms in patients with PPH is required.

## ACKNOWLEDGEMENT

The authors acknowledge Professor Neil B Pride, National Heart and Lung Institute, Hammersmith Hospital/Royal Brompton Hospital, London for most valuable and helpful discussions.

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## REFERENCES

- 1 **Peacock AJ**. Primary pulmonary hypertension. *Thorax* 1999;**54**:1107-18.
- 2 **Wagenvoort CA**, Wagenvoort N. Primary pulmonary hypertension. *Circulation* 1970;**57**:1163-84.
- 3 **Inscore SC**, Stenmark KR, Orton C, et al. Neonatal calves develop airflow limitation due to chronic hypobaric hypoxia. *J Appl Physiol* 1991;**70**:384-90.
- 4 **Lai YL**, Olson LW, Gillespie MN. Ventilatory dysfunction precedes pulmonary vascular changes in monocrotaline-treated rats. *J Appl Physiol* 1991;**70**:561-6.

- 5 **Wessel HU**, Kezdi P, Cugell DW. Respiratory and cardiovascular function in patients with severe pulmonary hypertension. *Circulation* 1964;**29**:825-32.
- 6 **Scharf SM**, Feldman NT, Graboyes TB, et al. Restrictive ventilatory defect in a patient with primary pulmonary hypertension. *Am Rev Respir Dis* 1978;**118**:409-13.
- 7 **Gazetopoulos N**, Salonikides N, Davies H. Cardiopulmonary function in patients with pulmonary hypertension. *Br Heart J* 1974;**36**:19-28.
- 8 **Horn M**, Ries A, Neveu C, et al. Restrictive ventilatory pattern in precapillary pulmonary hypertension. *Am Rev Respir Dis* 1983;**128**:163-5.
- 9 **Fernandez BP**, Lupi HE, Martinez-Guerra ML, et al. Peripheral airways obstruction in idiopathic pulmonary artery hypertension. *Chest* 1983;**83**:732-8.
- 10 **Burke CM**, Glanville AR, Morris AJ, et al. Pulmonary function in advanced pulmonary hypertension. *Thorax* 1987;**42**:131-5.
- 11 **Ewert R**, Opitz C, Wensel R, et al. Iloprost as inhalative or intravenous long-term treatment of patients with primary pulmonary hypertension. Registry of the Berlin Study Group for Pulmonary Hypertension. *Z Kardiol* 2000;**89**:987-99.
- 12 **Rich S**, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;**107**:216-23.
- 13 **Hoepfer MM**, Olschewski H, Ghofrani HA, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH Study Group. *J Am Coll Cardiol* 2000;**35**:176-82.
- 14 **Olschewski H**, Ghofrani A, Winkler J, et al. Therapy of life-threatening pulmonary hypertension with inhaled iloprost. *Ann Intern Med* 2000;**132**:443-53.
- 15 **Executive Summary of the World Symposium on PPH**. Available at <http://www.who.int/ncd/cvd/pph.html>, 1999 (accessed 1 November 2000).
- 16 **Quanjer PH**, Lebowitz MD, Gregg I, et al. Peak expiratory flow: conclusions and recommendations of a Working Party of the European Respiratory Society. *Eur Respir J Suppl* 1997;**24**:S2-8.
- 17 **Quanjer Ph**. EGKS: standardized lung function testing. *Bull Eur Physiopathol Respir* 1983;**19**(Suppl 5).
- 18 **Hoepfer MM**, Maier R, Tongers J, et al. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. *Am J Respir Crit Care Med* 1999;**160**:535-41.
- 19 **Altman DG**, Gore SM, Gardner MJ, et al. Statistical guidelines for contributors to medical journals. *BMJ* 1983;**286**:1489-93.
- 20 **Williams MH**, Adler JJ, Colp C. Pulmonary function studies as an aid in the differential diagnosis of pulmonary hypertension. *Am J Med* 1969;**47**:378-83.
- 21 **Pride NB**, Permutt S, Riley RL, et al. Determinants of maximal expiratory flow from the lungs. *J Appl Physiol* 1967;**23**:646-62.
- 22 **Meyer FJ**, Zugck C, Haass M, et al. Inefficient ventilation and reduced respiratory muscle capacity in congestive heart failure. *Basic Res Cardiol* 2000;**95**:333-42.
- 23 **Meyer FJ**, Borst MM, Zugck C, et al. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation* 2001;**103**:2153-8.
- 24 **Dinh-Xuan AT**, Higenbottam TW, Clelland C, et al. Impairment of endothelium-dependent pulmonary artery relaxation in chronic obstructive lung disease. *N Engl J Med* 1991;**324**:1539-47.
- 25 **Giaid A**, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995;**333**:214-21.
- 26 **Belvisi MG**, Stretton CD, Yacoub M, et al. Nitric oxide is the endogenous neurotransmitter of bronchodilator nerves in humans. *Eur J Pharmacol* 1992;**210**:221-2.
- 27 **Fagan KA**, McMurtry IF, Rodman DM. Role of endothelin-1 in lung disease. *Respir Res* 2001;**2**:90-101.
- 28 **Spiekerkoetter E**, Hoepfer MM, Fabel H. Acute hemodynamic effects of salbutamol aerosol in patients with primary pulmonary hypertension. *Am J Respir Crit Care Med* 2001;**163**:A541.
- 29 **O'Hagan AR**, Stillwell PC, Arroliga A. Airway responsiveness to inhaled albuterol in patients with pulmonary hypertension. *Clin Pediatr* 1999;**38**:27-33.
- 30 **Kindman LA**, Vagelos RH, Willson K, et al. Abnormalities of pulmonary function in patients with congestive heart failure, and reversal with ipratropium bromide. *Am J Cardiol* 1994;**73**:258-62.
- 31 **Uren NG**, Davies SW, Jordan SL, et al. Inhaled bronchodilators increase maximum oxygen consumption in chronic left ventricular failure. *Eur Heart J* 1993;**14**:744-50.