Peripheral airway obstruction in primary pulmonary hypertension

F J Meyer, R Ewert, M M Hoeper, H Olschewski, J Behr, J Winkler, H Wilkens, C Breuer, W Kübler, M M Borst for the German PPH Study Group

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/cm².

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 PAP-mean (r=0.31, p<0.001). In patients with PAP-mean 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.

Original Article

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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; \( r = 0.22; P = 0.002 \)), FEV1/VC (\( r = 0.24; P = 0.002 \)), maximal expiratory flows at 25%, 50%, and 75% of exhaled VC, respectively. \( * \) Student’s \( t \) test.

The FEV1/VC ratio in patients with PPH was significantly reduced compared with controls (table 1). Moreover, the prevalence of airflow obstruction with an FEV1/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), MEF25, MEF50, and MEF75 was seen compared with predicted values (table 1) and control subjects (fig 2).

Airflow limitation was more pronounced at lower values of VC. MEF25, MEF50, and MEF75 were reduced by 18%, 34%, and 44%, 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 FEV1/VC 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).

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

<table>
<thead>
<tr>
<th></th>
<th>PPH (n=171)</th>
<th>Controls (n=64)</th>
<th>Mean difference (95% CI)</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC (% predicted)</td>
<td>98 (12)</td>
<td>102 (17)</td>
<td>-4 (-7.9 to -0.1)</td>
<td>0.046</td>
</tr>
<tr>
<td>RV (% predicted)</td>
<td>118 (24)</td>
<td>109 (27)</td>
<td>9 (1.9 to 16.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV/TLC (% predicted)</td>
<td>117 (27)</td>
<td>97 (29)</td>
<td>20 (12.3 to 27.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rtot (% of upper limit)</td>
<td>98 (42)</td>
<td>91 (42)</td>
<td>7 (-5.1 to 19.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>VC (% predicted)</td>
<td>91 (16)</td>
<td>102 (10)</td>
<td>-11 (15.2 to -0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>83 (15)</td>
<td>106 (9)</td>
<td>-23 (-26.9 to -19.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/VC (%)</td>
<td>76 (8)</td>
<td>84 (5)</td>
<td>-8 (10.09 to -5.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEF (% predicted)</td>
<td>83 (21)</td>
<td>98 (12)</td>
<td>-13 (-18.5 to -7.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF25 (% predicted)</td>
<td>82 (24)</td>
<td>103 (13)</td>
<td>-21 (-27.2 to -14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF50 (% predicted)</td>
<td>66 (24)</td>
<td>101 (19)</td>
<td>-35 (-41.5 to -28.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MEF75 (% predicted)</td>
<td>46 (23)</td>
<td>82 (22)</td>
<td>-36 (-42.5 to -29.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; TLC = total lung capacity; RV = residual volume; Rtot = airway resistance; VC = vital capacity; FEV1 = forced expiratory volume in 1 second; PEF = peak expiratory flow; MEF25, MEF50, MEF75 = maximal expiratory flow at 25%, 50%, and 75% of exhaled VC, respectively. *Student’s \( t \) test.
Peripheral airway obstruction in PPH

Figure 3 To correct for differences in vital capacity (VC), a ratio of MEF75, MEF50, and MEF25 and the respective fraction of remaining VC, e.g. $\text{MEF}_{75} \times (0.75 \times \text{VC})$ 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 catheterisation, spirometric testing, and body plethysmography.

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. Similarly, the frequently used criteria for airway obstruction (FEV1/VC <70%, Rtot >0.3 kPa.s/l) were not met by our 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 airway obstruction may reflect the underlying vascular disease and its haemodynamic consequences. This concept is supported by experimental data and by a small study 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. Moreover, in PPH there is decreased endothelial synthesis of the vasodilator nitric oxide (NO) and increased levels of the vasoconstrictor endothelin-1 (ET-1) 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)

<table>
<thead>
<tr>
<th>PAPmean (mm Hg)</th>
<th>Mean difference (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;56 mm Hg</td>
<td>&gt;56 mm Hg</td>
<td></td>
</tr>
<tr>
<td>PA PAPmean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=86)</td>
<td>(n=85)</td>
<td></td>
</tr>
<tr>
<td>47 (7)</td>
<td>68 (12)</td>
<td>-21 [-23.9 to -18.1]</td>
</tr>
<tr>
<td>CVF (mm Hg)</td>
<td>6 (4)</td>
<td>-4 [-5.4 to -2.6]</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7 (3)</td>
<td>-1 [-1.9 to -0.1]</td>
</tr>
<tr>
<td>PVR (dyncs/cm²)</td>
<td>1029 (431)</td>
<td>-755 [-923.1 to -586.9]</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.6 (1.1)</td>
<td>-0.5 [0.2 to 0.9]</td>
</tr>
<tr>
<td>TLC [% predicted]</td>
<td>99 (18)</td>
<td>3 [-1.7 to 7.7]</td>
</tr>
<tr>
<td>RV [% predicted]</td>
<td>113 (33)</td>
<td>-9 [-18.8 to 0.8]</td>
</tr>
<tr>
<td>RV/TLC [% predicted]</td>
<td>111 (22)</td>
<td>-14 [-22.2 to -5.8]</td>
</tr>
<tr>
<td>Rtot [% of upper limit]</td>
<td>95 (46)</td>
<td>-6 [-18.8 to 6.8]</td>
</tr>
<tr>
<td>VC [% predicted]</td>
<td>94 (15)</td>
<td>7 [2.5 to 11.5]</td>
</tr>
<tr>
<td>FEV1 [% predicted]</td>
<td>87 (15)</td>
<td>7 (2.4 to 11.7)</td>
</tr>
<tr>
<td>FEV1/VC [%]</td>
<td>75 (8)</td>
<td>-2 [-4.7 to 0.7]</td>
</tr>
<tr>
<td>PEF [% predicted]</td>
<td>88 (21)</td>
<td>7 [0.7 to 13.3]</td>
</tr>
<tr>
<td>MEF75 [% predicted]</td>
<td>84 (23)</td>
<td>4 [-3.1 to 11.1]</td>
</tr>
<tr>
<td>MEF50 [% predicted]</td>
<td>66 (23)</td>
<td>0 [7.4 to 7.4]</td>
</tr>
<tr>
<td>MEF25 [% predicted]</td>
<td>46 (24)</td>
<td>0 [7.5 to 7.5]</td>
</tr>
</tbody>
</table>

CI = confidence interval; PAPmean = mean pulmonary artery pressure; CVF = central venous pressure; PCWP = postcapillary wedge pressure; PVR = pulmonary vascular resistance; TLC = total lung capacity; RV = residual volume; Rtot = airway resistance; VC = vital capacity; FEV1 = forced expiratory volume in 1 second; PEF = peak expiratory flow; MEF25, 50, 75 = 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 muscle. 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. 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 FEV1, VC or Rtof 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. 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. It also corresponds to data from patients with pulmonary hypertension secondary to CHF in whom the inhalation of ipratropium bromide improved FEV1, expiratory flow rates, and exercise limitation without affecting haemodynamics. Further evaluation of reversibility of peripheral airway obstruction and possible beneficial effects on exercise capacity and symptoms in patients with PPH is required.

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REFERENCES

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