

# Pulmonary function in advanced pulmonary hypertension

CONOR M BURKE, ALLAN R GLANVILLE, ADRIAN J R MORRIS,  
DANIEL RUBIN, JAMES A HARVEY, JAMES THEODORE, EUGENE D ROBIN

*From the Division of Respiratory Medicine, Stanford University Medical Center, Stanford, California, USA*

**ABSTRACT** Pulmonary mechanical function and gas exchange were studied in 33 patients with advanced pulmonary vascular disease, resulting from primary pulmonary hypertension in 18 cases and from Eisenmenger physiology in 15 cases. Evidence of airway obstruction was found in most patients. In addition, mean total lung capacity (TLC) was only 81.5% of predicted and 27% of our subjects had values of TLC less than one standard deviation below the mean predicted value. The mean value for transfer factor (TLCO) was 71.8% of predicted and appreciable arterial hypoxaemia was present, which was disproportionate to the mild derangements in pulmonary mechanics. Patients with Eisenmenger physiology had significantly lower values of arterial oxygen tension (PaO<sub>2</sub>) ( $p < 0.05$ ) and of maximum mid expiratory flow ( $p < 0.05$ ) and significantly higher pulmonary arterial pressure ( $p < 0.05$ ) than those with primary pulmonary hypertension, but no other variables were significantly different between the two subpopulations. It is concluded that advanced pulmonary vascular disease in patients with primary pulmonary hypertension and Eisenmenger physiology is associated not only with severe hypoxaemia but also with altered pulmonary mechanical function.

The availability of human heart-lung transplantation at our institution has led to the referral of a large number of patients with advanced pulmonary hypertension for consideration of surgery. So far 33 patients suffering from primary pulmonary hypertension or pulmonary hypertension secondary to congenital heart disease with Eisenmenger physiology have been studied in our pulmonary function laboratory (data from nine of them have been reported<sup>1</sup> but are included here and expanded to provide a more complete evaluation). Previous reports of similar patients have been limited to single case studies or small groups and have shown disparate results<sup>1-6</sup>; isolated reports of a restrictive ventilatory defect<sup>3</sup> and patients with airflow obstruction<sup>2</sup> have appeared.

Given this background, a larger series such as this one, in which patients were comprehensively studied in the same laboratory with a uniform protocol, should provide a more accurate assessment of lung function in patients with pulmonary hypertension.

## Methods

Thirty three patients suffering from advanced (stage IV, New York Heart Association) pulmonary vascular disease resulting from primary pulmonary hypertension (18 cases) and from congenital heart disease with Eisenmenger physiology (15 cases) were considered suitable for heart-lung transplantation after examination by at least two independent physicians who agreed that life expectancy in each case was probably less than 12 months. Cardiac catheterisation and pulmonary angiography were performed before referral in all cases. These were not repeated here in view of the associated morbidity and mortality. All clinical data, however, were reviewed in detail and patients with known causes of pulmonary hypertension other than congenital heart disease were excluded.

Ages ranged from 17 to 45 with a mean of 32 years, and there were 17 men and 16 women. Almost half of the patients were smokers, with a mean smoking history of 18 pack years. No patient had a history of asthma, and blood eosinophil counts were consistently within normal limits.

Pulmonary function was assessed by standard methods.<sup>1</sup> In brief, lung volumes, flow rates,

Address for reprint requests: Dr James Theodore, Stanford University School of Medicine, Department of Medicine, Stanford, California, 94305, USA.

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flow-volume loops, and transfer factor (TLCO) measurements were obtained by the use of a Collins DS/520 system. A Jaeger "Bodytest-Pneumotest" plethysmographic system was used to determine airway conductance (Gaw), intrathoracic gas volume, and specific airway conductance (sGaw). Predicted values were derived from the following sources: spirometry,<sup>7,8</sup> flow rates,<sup>9</sup> lung volumes,<sup>10</sup> arterial oxygen tensions (PaO<sub>2</sub>),<sup>11</sup> and carbon monoxide transfer factor (TLCO).<sup>12</sup> Predicted TLCO values were corrected for haemoglobin concentrations in each patient. The normal range for sGaw was derived from the data of Watanabe *et al.*<sup>13</sup> Individual manoeuvres were repeated at least three times to obtain reproducible results and the best values were recorded. Values for pulmonary arterial pressure were obtained from the patients' medical records, but it should be noted that the interval between cardiac catheterisation and pulmonary function testing ranged from two to 36 (mean 10) months.

Differences between patients with primary pulmonary hypertension and those with Eisenmenger physiology were studied by dividing the population into the two diagnostic subgroups and analysing any differences in the variables noted in table 1 between the two populations by Student's *t* test. Similarly, functional variables were compared between patients with higher (TLC < 1 SD below predicted) and lower (TLC more than 1 SD below predicted) lung volumes, greater (mean PAP > 50 mm Hg) and lesser (mean PAP ≤ 50 mm Hg) pulmonary hypertension, and greater (PaO<sub>2</sub> ≤ 60% predicted) and lesser (PaO<sub>2</sub> > 60% predicted) hypoxaemia. In addition, pulmonary function in patients with a history of cigarette smoking was compared with that in non-smokers.

## Results

Values of lung volumes, flows, sGaw, TLCO, arterial blood gases and mean pulmonary arterial pressure (PAP) for the entire group are listed in table 1. In addition to mean values, the data are tabulated according to the proportion lying outside 1 and 2 SDs from the mean in an attempt to represent the range of disease.

In the population as a whole lung volumes were in the low normal range, mean TLC being 81.5% and functional residual capacity 89.2% of predicted. About three quarters of the group had a TLC value within 1 SD of predicted; 27% and 6% had values less than 1 and 2 SDs of predicted. The effect of cardiomegaly on lung volumes was not assessed.

Dynamic variables were reduced, with mean FVC 73.2%, FEV<sub>1</sub> 72.6% and maximum mid expiratory flow (FEF<sub>25-75</sub>) 60.0% of predicted. In about half the patients FVC and FEV<sub>1</sub> were more than 1 SD below the predicted value, and FEF<sub>25-75</sub> was more than 1 SD below the predicted value in 82%. Thus effort independent flows at low lung volumes were more adversely affected than flows early in expiration. The mean FEF<sub>50</sub>/FVC ratio was only 68.6% of predicted, suggesting that the reduced flows were not related to reduced lung volumes.<sup>14</sup> Although the mean FEV<sub>1</sub>/FVC ratio was normal for the group, one fifth of patients had a ratio more than 1 SD below the predicted value. The mean sGaw for the group was in the low normal range, but 75% and 45% had values more than 1 and 2 SDs respectively below the predicted value.<sup>13</sup>

The mean TLCO for the entire population was 78% of predicted, and 70% of the patients had values more

Table 1 Pulmonary function in 33 patients with advanced pulmonary hypertension

	Mean (SD)	Range	Percentage of total population	
			> 1 SD below predicted	> 2 SD below predicted
TLC*	81.5 (13.0)	50-105	27	6
FRC*	89.2 (16.7)	41-125	12	6
FVC*	73.2 (16.5)	34-101	51	9
FEV <sub>1</sub> *†	72.6 (17.9)	31-112	45	9
FEF <sub>25-75</sub> *‡	60.0 (24.9)	17-106	82	36
FEF <sub>50</sub> /FVC*	68.6 (27.0)	28-137	67	39
TLCO*	78.0 (24.5)	26-120	70	33
FEV <sub>1</sub> /FVC*	101.3 (11.4)	82-121	21	6
sGaw†	0.17 (0.07)	0.05-0.34	75	45
PaO <sub>2</sub> ‡	58.1 (18.6)	27-93	87 (< 80 mm Hg)	58 (< 60 mm Hg)
PaCO <sub>2</sub> ‡	29.8 (4.1)	21-36	87 (< 35 mm Hg)	42 (< 30 mm Hg)
PAP (mean)‡	66.2 (22.8)	25-122	83 (> 40 mm Hg)	63 (> 60 mm Hg)

\*% predicted.

†l<sup>-1</sup>/s<sup>-1</sup>.

‡mm Hg (= 0.13 kPa).

TLC—total lung capacity; FRC—functional residual capacity; FVC—forced vital capacity; FEF<sub>25-75</sub>—maximum mid expiratory flow between 25% and 75% of vital capacity; TLCO—carbon monoxide transfer factor; sGaw—specific airway conductance; PaO<sub>2</sub>, PaCO<sub>2</sub>—arterial oxygen and carbon dioxide tension; PAP—pulmonary arterial pressure.

than 1 SD below the predicted value. Pulmonary gas exchange was significantly impaired, and mean  $\text{PaO}_2$  and  $\text{PaCO}_2$  were 58 and 30 mm Hg (7.7 and 4.0 kPa) respectively. Thirteen per cent of the group had a  $\text{PaO}_2$  of 80 mm Hg (10.7 kPa) or more (all with primary pulmonary hypertension), and the alveolar-arterial oxygen difference (calculated using the alveolar air equation with direct measurement of respiratory exchange ratio,  $\dot{V}\text{CO}_2/\dot{V}\text{O}_2$ , and arterial blood gas tensions) was increased (more than 25 mm Hg (3.3 kPa)) in all these patients. Thus the normal  $\text{PaO}_2$  found in some patients with primary pulmonary hypertension was achieved only by alveolar hyperventilation, and calculation of the alveolar arterial oxygen difference provided evidence of impaired gas exchange despite normal arterial oxygen tensions. Alveolar hyperventilation was present in all cases, and almost half the group had  $\text{PaCO}_2$  values less than 30 mm Hg (7.5 kPa).

The group as a whole therefore had considerable pulmonary hypertension, appreciable impairment of gas exchange, reduced TLC and lung volumes, and evidence of airflow obstruction at low lung volumes.

Comparison of functional variables between patients with primary pulmonary hypertension and those with Eisenmenger physiology (table 2) showed that mean PAP was significantly higher ( $p < 0.05$ ) and mean  $\text{PaO}_2$  and  $\text{FEF}_{25-75}$  significantly lower ( $p < 0.05$ ) in the group with Eisenmenger physiology. None of the other variables were significantly different between the two subpopulations.

In an attempt to identify a possible relationship between lung volumes and flows, the population as a whole was separated into two groups defined by TLC. In the group whose TLC was within 1 SD of the

predicted value,  $\text{FEV}_1$ ,  $\text{FEV}_1/\text{FVC}$ ,  $\text{FEF}_{25-75}$ , and sGaw were not significantly different from the group whose TLC was more than 1 SD below the predicted value. In addition, no significant correlation was found between TLC and  $\text{FEV}_1$ ,  $\text{FEV}_1/\text{FVC}$ ,  $\text{FEF}_{25-75}$ , or sGaw. The alterations of flow characteristics therefore appear not to be volume related.

Patients with a history of smoking were not significantly different in any of the variables (see summary in table 2) from non-smokers. Similarly, when the population was divided into subgroups defined by either PAP or  $\text{PaO}_2$ , no significant difference in pulmonary mechanical function was seen between those with relatively greater ( $\text{PaO}_2 \leq 60\%$  of predicted) and those with lesser degrees ( $\text{PaO}_2 > 60\%$  of predicted) of hypoxaemia or between those with a relatively higher ( $> 50$  mm Hg) and those with a lower ( $\leq 50$  mm Hg) mean PAP.

## Discussion

This study expands previous reports of individual patients with pulmonary hypertension and concomitant obstructive or restrictive ventilatory defects.<sup>1-6</sup> The reduced flows were not explained by the reduced lung volumes since the mean  $\text{FEF}_{50}/\text{FVC}$  ratio was only 68.6% of predicted and comparison between subgroups with normal (within 1 SD of predicted) and reduced TLC revealed no significant differences in flows, which were equally reduced in the two subgroups. The reduced  $\text{FEF}_{25-75}$  and  $\text{FEF}_{50}/\text{FVC}$  values, with the relatively well preserved  $\text{FEV}_1/\text{FVC}$  ratio seen in most cases, is suggestive of an obstructive process primarily affecting the peripheral airways.

Table 2 Functional variables in 18 patients with primary pulmonary hypertension and 15 patients with Eisenmenger physiology

	Primary pulmonary hypertension		Eisenmenger physiology	
	Mean (SEM)	Range	Mean (SEM)	Range
TLC*	82.2 (2.3)	69-98	80.9 (3.7)	50-105
FRC*	87.4 (2.9)	71-104	90.6 (4.8)	41-125
FVC*	74.9 (3.4)	53-101	71.8 (4.5)	34-98
$\text{FEV}_1$ *	77.3 (4.2)	46-112	68.7 (4.4)	31-95
$\text{FEF}_{25-75}$ *	70.3 (6.6)	31-101	52.2 (5.3)	17-106
$\text{FEF}_{50}/\text{FVC}$ *	76.5 (6.5)	51-131	61.8 (6.8)	28-137
TLCo*	71.8 (6.7)	26-111	83.7 (6.0)	40-120
$\text{FEV}_1/\text{FVC}$ *	105.8 (2.9)	82-121	96.7 (3.2)	83-119
sGaw†	0.18 (0.02)	0.05-0.31	0.16 (0.02)	0.06-0.34
** $\text{PaO}_2$ ‡	72.1 (3.9)	41-93	46.6 (3.1)	27-74
$\text{PaCO}_2$ ‡	28.9 (1.0)	23-35	30.5 (1.0)	21-36
§PAP (mean)‡	57.8 (6.3)	25-122	74.5 (4.6)	26-93

\*% predicted.

\*\*Significantly lower in EP group ( $p < 0.05$ ).

† $\text{l}^{-1}/\text{s}^{-1}$ .

‡mm Hg (= 0.13 kPa).

§Significantly lower in PPH group ( $p < 0.05$ ).

Abbreviations as in table 1.

Since dyspnoea is a common presenting symptom in pulmonary hypertension, the finding of abnormal pulmonary mechanics may suggest a primary diagnosis of intrinsic lung disease. In our group, however, the severe dyspnoea and the considerable hypoxaemia were clearly disproportionate to the degree of derangement of pulmonary mechanical function.

The failure to find a correlation between smoking history and lung function is at first sight surprising. This finding may be explained by the fact that only a minority of smokers develop airflow limitation demonstrable by the techniques used here. In addition, all of our patients had ceased smoking at least three years before the study. Undue emphasis should not be placed on the absence of any correlation between PAP and pulmonary functional indices in this group in view of the long interval (mean 10 months) between cardiac catheterisation and lung function tests.

Despite the severe hypoxaemia, TLCO was relatively well preserved (mean 78% predicted). This finding is in keeping with previous reports of patients with pulmonary hypertension secondary to pulmonary vascular disease, and contrasts with the severe impairment of diffusion capacity seen in patients with pulmonary hypertension resulting from parenchymal lung disease.<sup>1,5</sup>

Arterial hypoxaemia was almost invariably present (mean  $P_{aO_2}$  58 mm Hg (7.7 kPa)) and  $P_{aO_2}$  was greater than 80 mm Hg (10.7 kPa) in only 13% of cases. Right to left intracardiac shunting is the obvious explanation for hypoxaemia in the group with Eisenmenger physiology. Potential mechanisms to explain arterial hypoxaemia in patients with primary pulmonary hypertension include shunting through a patent foramen ovale, ventilation/perfusion ( $\dot{V}_A/\dot{Q}_C$ ) inequalities, and reductions in mixed venous  $P_{O_2}$  as a result of a low cardiac output,<sup>15</sup> which would further enhance the effects of  $\dot{V}_A/\dot{Q}_C$  mismatching on gas exchange.

Our population included 18 patients with primary pulmonary hypertension and 15 with Eisenmenger physiology. The latter group included patients with a wide variety of congenital heart lesions whose only common feature was the presence of Eisenmenger physiology. Since the small numbers of patients precluded any meaningful comparison of individual heart lesions, we simply compared those with primary pulmonary hypertension and with Eisenmenger physiology. Not surprisingly, in view of their anatomical shunts, the latter group had a significantly lower mean  $P_{aO_2}$ . In addition, mean  $FEF_{25-75}$  was significantly lower ( $p < 0.05$ ) in the group with Eisenmenger physiology.

The precise pathogenetic mechanism responsible for altered pulmonary function described in this and

other reports of patients with pulmonary hypertension is not clear. Changes in lung compliance have however been reported both in patients and animal models with altered pulmonary haemodynamics<sup>2,3,16,17</sup> presumably resulting from mechanical coupling of the vascular and air spaces. Although we did not measure pressure volume relationships in our patients, the observed functional derangement might result from a similar mechanism. Alternatively, it has been postulated that patients such as these may develop mechanical alterations as a result of ischaemic lung disease, but data to support this hypothesis are not currently available.<sup>18</sup> Although low grade bronchitis and bronchiolitis have been described in patients with primary pulmonary hypertension who had evidence of airflow limitation, the basis for these changes is not clear, and they do not appear to be due to an increased incidence of respiratory tract infections.<sup>2</sup>

In conclusion, advanced pulmonary vascular disease resulting from primary pulmonary hypertension and from Eisenmenger physiology appears to be associated with appreciable disturbance of pulmonary function. Most of our patients had evidence of airway obstruction, and mean TLC was only 81.5% of predicted. Hypoxaemia was almost invariably present and disproportionate to the relatively minor mechanical abnormalities. Alveolar hyperventilation was seen in all cases. Patients with Eisenmenger physiology had greater mean PAP and lower values of  $P_{aO_2}$  and  $FEF_{25-75}$  than those with primary pulmonary hypertension, despite similar levels of disability. Further insight into pathophysiological mechanisms responsible for these functional changes could best be gained by detailed analysis of pressure-volume relationships and morphometric studies. Whatever mechanisms are operative, our data confirm that obstructive and restrictive ventilatory defects are common in patients with pulmonary vascular disease.

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## References

- 1 Theodore J, Jamieson SW, Burke CM, *et al.* Physiologic aspects of human heart-lung transplant. Pulmonary function status of the post-transplant lung. *Chest* 1984;**86**:349-57.
- 2 Fernandez-Bonetti P, Lupi-Herrera E, Martinez-Guerra ML, Barrios R, Seoane M, Sandoval J. Peripheral airways obstruction in idiopathic pulmonary artery hypertension. *Chest* 1983;**83**:732-8.
- 3 Scharf SM, Feldman NT, Graboyes TB, Wellman JJ.

- Restrictive ventilatory defect in a patient with primary pulmonary hypertension. *Am Rev Respir Dis* 1978; **118**:409–13.
- 4 D'Alonzo GE, Bower JS, Dantzker DR. Differentiation of patients with primary and thromboembolic pulmonary hypertension. *Chest* 1984; **85**:457–61.
- 5 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.
- 6 MacArthur CGC, Hunter D, Gibson GJ. Ventilatory function in the Eisenmenger syndrome. *Thorax* 1979; **34**:348–53.
- 7 Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis* 1971; **103**:57–67.
- 8 Morris JF, Temple WF, Koski A. Normal values for the ratio of one-second forced expiratory volume to forced vital capacity. *Am Rev Respir Dis* 1973; **108**:1000–3.
- 9 Cherniack RM, Raber MB. Normal standards for ventilatory function using an automated wedge spirometer. *Am Rev Respir Dis* 1972; **106**:38–45.
- 10 Boren HG, Kory RC, Syner JC. The Veterans Administration-Army cooperative study of pulmonary function. II. The lung volume and its subdivision in normal men. *Am J Med* 1966; **41**:96–114.
- 11 Sorbini CA, Grassi V, Solinas E, Muiesan G. Arterial oxygen tension in relation to age in healthy subjects. *Respiration* 1968; **25**:3–13.
- 12 Bates DV, Macklem PT, Christie RV, eds. *Respiratory function in disease*. Philadelphia: WB Saunders, 1971:93–4.
- 13 Watanabe S, Renzetti AD jun, Begin R, Bigler AH. Airway responsiveness to a bronchodilator aerosol. I. Normal human subjects. *Am Rev Respir Dis* 1974; **109**:530–7.
- 14 Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-volume curve. Normal standards, variability and effects of age. *Am Rev Respir Dis* 1976; **113**:587–600.
- 15 Dantzker DR, Bower JS. Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. *J Clin Invest* 1979; **64**:1050–5.
- 16 Giannelli S, Ayres SM, Buehler ME. Effect of pulmonary blood flow upon lung mechanics. *J Clin Invest* 1967; **46**:1625–42.
- 17 Hauge A, Bo G, Waaler BA. Interrelations between pulmonary liquid volumes and lung compliance. *J Appl Physiol* 1975; **38**:608–14.
- 18 Robin ED, Theodore J. Ischemic lung disease, including a new look at  $\dot{V}_A/\dot{Q}_C$ . *Chest* 1982; **82**:659–61.