

# Pulmonary vascular structure and function in chronic obstructive pulmonary disease

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**ABSTRACT** Cardiac catheterisation data from eight patients with severe chronic obstructive lung disease and pulmonary hypertension at rest ( $> 25$  mm Hg) were compared with those obtained from 14 patients with mild to moderate disease whose pulmonary artery pressure was within the normal range at rest (mean 15 (SEM 1) mm Hg), but increased with exercise (30 (2) mm Hg). We obtained lung sections from necropsy material from the group with severe disease, and from surgical specimens in the group with mild to moderate disease, and compared the structure of the vasculature in these groups with that obtained from surgical specimens in a non-smoking control group of seven patients. Oxygen administration either at rest or during exercise did not greatly affect the pulmonary arterial pressures. When cardiac index was plotted against pulmonary artery pressure at rest and during exercise and extrapolated to the axis there was no evidence for a critical closing pressure in either group. The vessels in the groups with mild to moderate and severe chronic obstructive lung disease showed intimal thickening (each 19% (SD 0.5%)) by comparison with the non-smoking group (16% (0.5%)). The group with severe disease, in addition, had medial hypertrophy (27% (0.5%) versus 24% (SD 1%) in the non-smoking group). These data are consistent with the idea that the diseased vessels are distorted and rigid. The lack of effect of breathing oxygen on the vascular response at rest and during exercise suggests that hypoxic vasoconstriction has a minimal role in the pulmonary hypertension of chronic obstructive lung disease. The data suggest that the intimal changes could narrow the vessel calibre in those patients with mild to moderate disease, and that the thickened media present in the vessels from patients with severe disease may act in concert with the enlarged intima to produce more severe vascular obstruction.

Although the association between chronic obstructive airways disease and pulmonary hypertension is well recognised, the exact nature of this association remains obscure. Theoretical possibilities include emphysematous destruction of the pulmonary vascular bed,<sup>1</sup> loss of elastic recoil with an increase in the critical opening pressure of the pulmonary vessels,<sup>2</sup> hypoxic constriction of the muscular pulmonary arteries,<sup>3,4</sup> increased alveolar and intrathoracic pressure secondary to airways obstruction,<sup>4,10</sup> and decreased vascular calibre and distensibility secondary to hyperplasia and hypertrophy of the vessel intima and media.<sup>2</sup> The small pulmonary arteries have been

identified to be the site of increased flow resistance in acute hypoxic states,<sup>3</sup> and have been shown to be altered morphologically in states of chronic hypoxia and in chronic airflow obstruction.<sup>4-6</sup>

The purpose of the present study was to examine the vasculature of patients with chronic airflow obstruction with and without resting pulmonary hypertension, and to compare these data with those from a group of lifetime non-smokers. We also wished to compare cardiac catheterisation data from patients with and without pulmonary hypertension, and relate these data to the vasculature structure.

## Methods

### SELECTION OF PATIENTS

The subjects were obtained from two sources. Necropsy material was obtained from eight patients enrolled in the nocturnal oxygen therapy trial, the sole criterion for selection being the presence of pulmonary

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hypertension (pulmonary artery pressure  $\geq 25$  mm Hg) at rest in room air. The remaining 21 subjects were patients who underwent lobectomy or pneumonectomy for isolated lung lesions at St Paul's Hospital, Vancouver. All patients except the group of seven non-smokers underwent right heart catheterisation and haemodynamic studies either before surgery or in the months preceding death. The subjects were divided into three groups: (1) a control group consisting of seven non-smokers; (2) a group of 14 patients with pulmonary artery pressures within the normal range at rest who had evidence of mild to moderate airflow obstruction but had oxygen tensions ( $\text{Po}_2$ ) of 55 mm Hg or more (mild to moderate disease group); and (3) a group of eight patients with pulmonary hypertension at rest, evidence of severe airflow obstruction, and also  $\text{Po}_2$  below 55 mm Hg (severe disease group).

Details of the cardiac catheterisation and pulmonary function procedures have been previously reported.<sup>57</sup> In brief, subjects had pulmonary artery pressure, pulmonary artery wedge pressure, heart rate, and cardiac output measured in a supine position: (1) with the patient resting and breathing room air, (2) after 10–30 minutes breathing 100% oxygen at rest, (3) after at least 10 minutes of supine exercise using a modified bicycle ergometer while breathing room air, and (4) after similar exercise breathing 100% oxygen. There was a slightly different exercise load in the two populations: the eight patients in the nocturnal oxygen therapy trial exercised to a load of 25 watts<sup>7</sup> and the thoracotomy group to 85% of the predicted maximal heart rate.<sup>5</sup> An estimate of critical closing pressure was obtained by plotting the cardiac index and pulmonary artery pressure at rest and during exercise and extrapolating this value to the intercept. Lung volumes were measured with a pressure compensated body plethysmograph and expiratory volumes were measured spirometrically. Transpulmonary pressure was determined by comparing oesophageal pressure measured with a balloon technique with mouth pressure on a differential pressure transducer (Validyne MP 45-1; range  $\pm 100$  cm  $\text{H}_2\text{O}$ ).

#### HISTOLOGICAL STUDIES

All of the lung specimens were inflated via the bronchial tree with either 10% formalin or 3% buffered glutaraldehyde at 25 cm  $\text{H}_2\text{O}$  pressure. They were fixed for 24 hours, and then sliced into 1 cm sagittal sections. Emphysema was assessed by a modification of the method of Thurlbeck *et al.*<sup>8,9</sup> With a template to allow for calculation of tissue shrinkage, six stratified random blocks were taken from the medial and lateral slices (surgical specimens) and 10 blocks were obtained from the parasagittal slices (necropsy specimens). The tissue samples were processed for histological examination in the usual fashion,

cut at 5  $\mu\text{m}$ , and stained with Verhoeff's elastic stain. The slides were examined without knowledge of subject group.

All muscular arteries of less than 1200  $\mu\text{m}$  external diameter with complete external and internal elastic lamina were traced with a camera lucida apparatus and an Apple II linked digitising board. An example of a vessel is illustrated in figure 1a. The reproducibility of the results was checked by remeasuring 58 vessels; concordance between the two sets of measurements was very good (0.97,  $p < 0.001$ ). The adventitia, the external and internal elastic lamina, and the luminal surface were outlined, and in addition the external diameter was measured by a line projected perpendicular to the greatest longitudinal diameter and was defined as the distance between adventitial borders (fig 1b). The total tissue area was calculated by subtracting luminal area from total area, defined as the area encompassed by the adventitial borders. The areas occupied by intima, muscularis, and adventitia were computed, and expressed as a percentage of the total tissue area.

#### STATISTICS

The cardiac catheterisation measurements were compared between the groups by means of an unpaired *t* test and within the groups by means of a paired *t* test, and the histological measurements were compared by using a nested analysis of variance with the nesting in the subjects and in the group.<sup>10</sup> The vessels of each group were then subdivided on the basis of the external vascular diameter into those of 0.4 mm or less, 0.41–0.8 mm, and 0.81–1.2 mm. Differences between groups were assessed by means of an analysis of variance. All statistically significant results of the analyses were corrected for multiple comparisons.

#### Results

##### PULMONARY FUNCTION

There were substantial differences in lung volumes among the groups. The group with severe disease had a greater total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) than the non-smokers and the group with mild to moderate disease ( $p < 0.001$ ). The latter two groups did not differ in lung volumes. Both groups with airways disease had lower flow rates than the non-smoking group (table 1). In addition, the group with severe disease had much lower values than the group with mild to moderate disease (table 1).

The patients with severe disease had significantly higher emphysema scores (mean 56 (SEM 8, range 15–75) than the group with mild to moderate disease (19 (5), range 0–60;  $p < 0.001$ ). The  $\text{Po}_2$  of the group with severe disease was decreased—49 (2) compared with

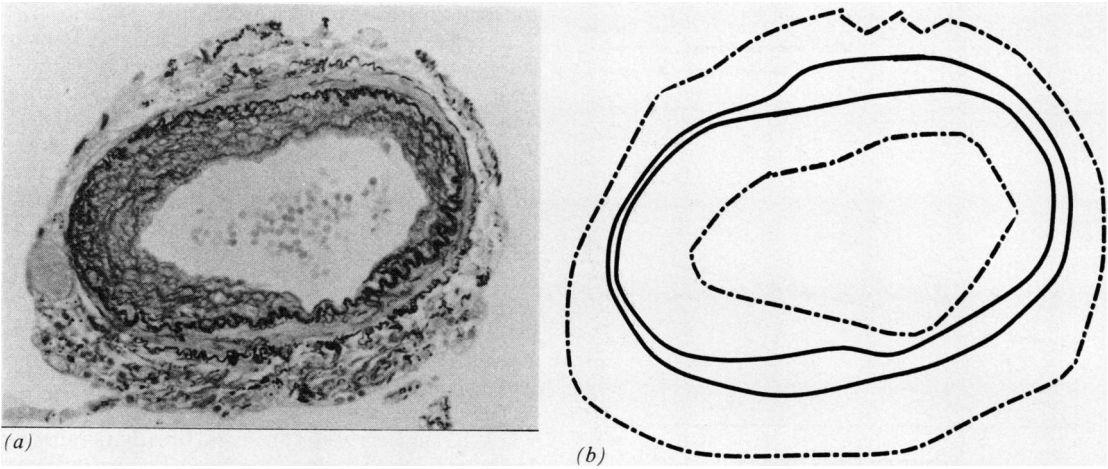


Fig 1 (a) Pulmonary artery with thickened media and intima. (Verhoeff elastic stain). (b) Crude illustration of the method of measuring the proportions of vessel intima and media by using a computer linked digitiser. In practice, the crinkles in the elastic lamina can be following relatively accurately. Circumferences are traced along adventitia, external and internal elastic lamina, and the inner aspect of intima.

Table 1 Pulmonary function and cardiac catheterisation data (means with standard errors in parentheses)

|  | Non-smokers | Mild to moderate disease | Severe disease |
|--|-------------|--------------------------|----------------|
| Sex: M/F                                       | 0/7         | 13/1                     | 8/0            |
| Age (y)  | 58 (5)      | 61 (2)                   | 65 (2)         |
| Pack years                                     | 0           | 60 (8)                   | 46 (2)         |
| Oxygen tension (mm Hg)                         | 90 (13)     | 75 (3)***                | 49 (2)+++      |
| Emphysema score                                | 0           | 19 (5)***                | 56 (8)+++      |
| TLC (% pred)                                   | 100 (2)     | 107 (3)***               | 143 (9)+++     |
| FRC (% pred)                                   | 109 (7)     | 127 (5)***               | 208 (20)+++    |
| RV (% pred)                                    | 105 (6)     | 141 (5)***               | 278 (36)+++    |
| FEV <sub>1</sub> (% pred)                      | 105 (6)     | 73 (4)***                | 30 (8)+++      |
| FEV <sub>1</sub> /FVC                          | 80 (2)      | 68 (2)***                | 38 (4)+++      |
| Ppa (mm Hg):                                   |             |                          |                |
| Rest, room air                                 |             | 15 (1)***                | 33 (3)         |
| Exercise, room air                             |             | 30 (2)***                | 53 (4)         |
| Rest, oxygen                                   |             | 16 (1)***                | 33 (3)         |
| Exercise, oxygen                               |             | 27 (2)***                | 49 (4)         |
| Ppaw (mm Hg):                                  |             |                          |                |
| Rest, room air                                 |             | 8 (1)                    | 11 (1)         |
| Exercise, room air                             |             | 15 (2)                   | 22 (3)         |
| Rest, oxygen                                   |             | 9 (1)                    | 12 (2)         |
| Exercise, oxygen                               |             | 11 (2)                   | 21 (3)         |
| PVR (dynes/cm <sup>2</sup> /s <sup>-1</sup> ): |             |                          |                |
| Rest, room air                                 |             | 145 (30)***              | 399 (63)       |
| Exercise, room air                             |             | 142 (28)***              | 399 (36)       |
| Rest, oxygen                                   |             | 140 (38)***              | 354 (55)       |
| Exercise, oxygen                               |             | 132 (22)***              | 347 (55)       |
| Cardiac index (l/min/m <sup>2</sup> ):         |             |                          |                |
| Rest, room air                                 |             | 2.92 (0.24)              | 2.92 (0.41)    |
| Exercise, room air                             |             | 5.87 (0.72)*             | 3.76 (0.32)    |
| Rest, oxygen                                   |             | 3.01 (0.23)              | 2.67 (0.23)    |
| Exercise, oxygen                               |             | 6.01 (0.64)*             | 3.67 (0.33)    |

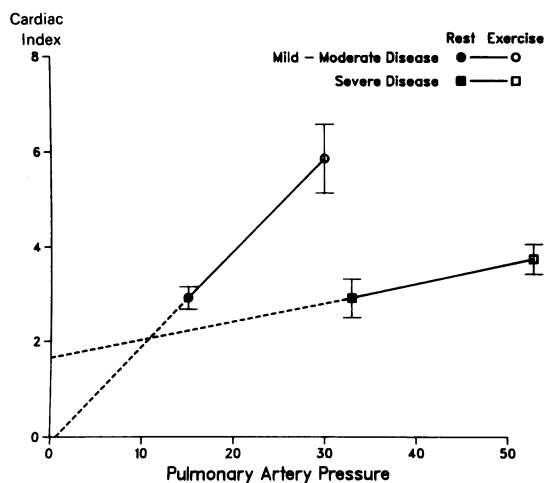
Difference from group with severe disease: \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001. Difference from non-smokers: †p < 0.05, ††p < 0.001. TLC—total lung capacity; FRC—functional residual capacity; RV—residual volume; FVC—forced vital capacity; Ppa—pulmonary artery pressure; Ppaw—pulmonary artery wedge pressure; PVR—pulmonary vascular resistance.

90 (13) mm Hg (6.5 (0.3) and 12 (1.7) kPa) (p < 0.001) in the non-smoking group and 75 (3) mm Hg (10 (0.4) kPa) (p < 0.001) in the mild to moderate disease group.

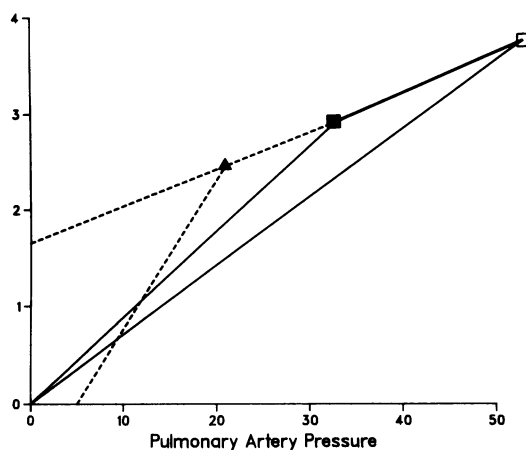
CARDIAC CATHETERISATION

The cardiac catheterisation data are shown in table 1 and figure 2a. The mean pulmonary artery pressures at rest were 15 (SEM 1) mm Hg in the mild to moderate disease group and 33 (3) mm Hg (p < 0.001) in the group with severe disease. The pulmonary artery wedge pressures were within the normal range in both groups—11 (1) mm Hg in the group with severe disease and 8 (1) mm Hg in the mild to moderate disease group. Breathing oxygen at rest had no effect on these pressures.

Exercise in room air increased the mean pulmonary artery pressure from 15 (SEM 1) to 30 (2) mm Hg (Δ P = 15 (2)) in the group with mild to moderate disease and from 33 (3) to 53 (4) mm Hg (Δ P = 20 (4)) in the group with severe disease; the pressure increases were not significantly different between the two groups. Exercise during oxygen breathing increased the pulmonary artery pressure from 16 (1) to 27 (2) mm Hg (Δ P = 11 (2)) in the group with mild to moderate disease. The pressure increases during exercise were different (p < 0.05) in the group with mild disease in room air (15 (2) mm Hg) and in oxygen (11 (2) mm Hg); in the group with severe disease exercise in oxygen increased the pulmonary artery pressure from 33 (3) to 49 (4) mm Hg (Δ P = 16 (4)), which was not different from



(a)



(b)

Fig 2 (a) Relationship between cardiac index (expressed in  $l/min/m^2$ ) and pulmonary artery pressure (expressed in mm Hg), at rest and during exercise in room air (values are means and standard errors). For the severe disease group the slope of the line measures 0.04 and the y intercept is 1.65. In the mild to moderate disease group the slope of the line measures 0.20, and the y intercept is -0.15. (b) The potential mechanism occurring in the lungs of patients with pulmonary hypertension due to emphysema and airways disease. The thick line repeats the data illustrated for this group in figure 2a. The filled square represents the datum point at rest, and the open square represents the datum point during exercise. Resistance for each point is calculated by a line passing through the origin (thin lines). Critical closure is calculated by extrapolation of the points to the line of intersection (dotted line). In this experiment a critical closure pressure cannot be calculated by this method, and it is likely that at a lower pressure, represented here by a triangle, there is a precipitous drop in flow (dotted line).

the increase observed with exercise in room air.

Exercise in room air increased the mean pulmonary artery wedge pressure from 8 (SEM 1) to 15 (2) mm Hg ( $\Delta P = 8$  (2)) in the mild to moderate disease group and from 11 (1) to 22 (3) mm Hg ( $\Delta P = 12$  (2)) in the group with severe disease. Exercise during oxygen breathing reduced the pulmonary artery wedge pressure by 4 mm Hg in the mild to moderate disease group but had no effect in the severe disease group (for differences between groups  $p < 0.01$ ).

The pulmonary vascular resistance in the group with severe disease was substantially increased ( $p < 0.001$ ) over the values noted in the mild to moderate disease group. Neither exercise nor oxygen breathing had a significant effect on these values.

The cardiac index was similar in the two groups when the subjects were at rest and breathing room air. In the group with mild to moderate disease it rose on exercise to a higher value than it did in the group with severe disease ( $p < 0.05$ ). Breathing oxygen did not change the cardiac index in either group, either at rest or during exercise. When the cardiac index was plotted against the pulmonary artery pressure in an attempt to assess the critical closing pressure (fig 2a) the group with severe disease showed an intercept on the flow axis at  $1.65 l/min/m^2$ , with virtually no change in flow with increasing pressure. In the mild to moderate disease group the extrapolation crossed the pressure axis close to zero, with an intercept of -0.15 on the flow axis and a steeper slope.

#### MORPHOMETRIC DATA

The nested analysis of variance, which corrects for within case as well as within group variation, showed that the cases with severe disease had greater mean percentage of media (27 (SEM 0.5)) than the non-smokers (24 (1)), and the mild to moderate disease group (19 (0.5)). Both groups with disease had a greater percentage of intima than the non-smokers (non-smokers 16% (0.5%) v 19% (0.5%) for each of the groups with mild to moderate and severe disease (in each case  $p < 0.001$ )).

Table 2 shows the data for the three groups when the vessels are divided into groups based on the external diameter. Three hundred and sixteen vessels were examined in the non-smoking group, 451 in the group with mild to moderate disease, and 900 in the group with severe disease. Sixty two per cent of vessels were in the size range of less than 0.4 mm in the non-smoking group, and the mild to moderate and severe disease groups had respectively 55% and 60% of vessels in this range. All three groups showed similar amounts of tissue in each of the size categories. The vessel wall components were, however, different; the severe disease group having a larger percentage of both intima and media than the non-smoking group.

Table 2 Vessel morphometry (means with standard errors in parentheses)

| Diameter (mm)                         | ≤ 0.4       | 0.41–0.8    | 0.81–1.2    |
|---------------------------------------|-------------|-------------|-------------|
| Total tissue area (mm <sup>2</sup> ): |             |             |             |
| Non-smokers                           | 0.10 (0.01) | 0.43 (0.05) | 0.81 (0.12) |
| Mild-moderate disease                 | 0.12 (0.01) | 0.34 (0.02) | 0.82 (0.06) |
| Severe disease                        | 0.11 (0.01) | 0.42 (0.02) | 0.84 (0.07) |
| Percentage of media:                  |             |             |             |
| Non-smokers                           | 23 (1.1)    | 26 (1.3)    | 24 (1.1)    |
| Mild-moderate disease                 | 18 (0.3)*** | 19 (0.4)*** | 19 (0.8)*   |
| Severe disease                        | 27 (0.6)    | 25 (0.5)    | 27 (1.5)*   |
| Percentage of intima:                 |             |             |             |
| Non-smokers                           | 16 (0.7)    | 16 (0.8)    | 15 (1.1)    |
| Mild-moderate disease                 | 21 (0.3)*** | 18 (0.5)*   | 14 (0.8)    |
| Severe disease                        | 19 (0.5)*** | 18 (0.5)**  | 20 (1.2)**  |

Difference from non-smokers: \*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001.

The mild to moderate disease group also showed differences in the percentage of intima, which appeared to be increased at the expense of the percentage of media.

In the non-smoking and severe disease groups, the percentage of vessel composed of intima and media remained relatively constant regardless of the size range. In the mild to moderate disease group the percentage media remained constant, but the percentage of intima decreased in the larger vessels.

## Discussion

This study extends our previously reported data in mild to moderate chronic obstructive lung disease<sup>5</sup> to include a new group of patients with end stage disease. The catheterisation data show that the pulmonary vasculature of patients with mild to moderate disease responds to oxygen during exercise but not at rest, while those with severe disease show no such response. When the vessels from these patients were compared with those from normal non-smoking subjects, those with mild to moderate disease showed a thickened intima while those with severe disease showed thickening of both intima and media.

Normally, exercise in the supine position is associated with only a slight increase (4–6 mm Hg) in pulmonary artery pressure. On the other hand, patients with mild and moderate chronic obstructive airways disease experienced a significant rise in pulmonary artery pressure and pulmonary artery wedge pressure with exercise.<sup>5</sup> When these patients were divided on the basis either of airways obstruction or of the severity of emphysema these pressure increments were abolished by oxygen in those with more airways obstruction or emphysema.

At the time of our previous study<sup>5</sup> we proposed that the difference in time constants between the patients' peripheral lung units and chest wall resulted in a rise in mean intrathoracic pressures during exercise and that this caused the rise in pulmonary artery pressure and pulmonary artery wedge pressure. We also suggested that oxygen breathing relieved the airways obstruction, resulting in a fall in intrathoracic pressure, and accounted for the equal fall in pulmonary artery pressure and pulmonary artery wedge pressure. Subsequent work by Albert and colleagues,<sup>11</sup> however, has shown that during upright exercise changes in pulmonary artery wedge pressure are not explained by changes in pleural pressure, which suggests that the changes we observed may have occurred because of a slower rate of breathing in oxygen.

Burton introduced the concept of critical closure to explain the observation that systemic vessels that are wide open and rigid at high pressures become unstable and close at positive pressure when the pressure falls.<sup>12,13</sup> He thought that this occurred in vessels that had smooth muscle tone because of Laplace's law. Permutt and colleagues applied this concept to the lung and carried out experiments that showed that the muscle tone in the arterioles could lead to closure and derecruitment of the alveolar vessels they supply.<sup>14</sup> The presence of excess tone in pulmonary arterioles of patients with airways obstruction could derecruit their pulmonary vessels and raise vascular pressures by decreasing the cross sectional area of the vascular bed. A similar result might occur in patients with emphysema if the decreased elastic recoil allowed the extra-alveolar vessels to close. Mink *et al.*,<sup>2</sup> using an animal model of emphysema, found a decrease in vascular compliance associated with an increased pressure for vascular recruitment, findings consistent with the above hypothesis. Extrapolation of the pressure-flow data in the pressure axis in our experiment does not result in a positive pressure for either the grouped data (fig 2a) or individual experiments (data not shown). Similar results are seen when the data of Emergil *et al.*<sup>15</sup> and Lockhart *et al.*<sup>16</sup> are plotted in this fashion. These data suggest that closure does not occur as pressure falls, which does not support the idea that vascular closure accounts for much of the observed pulmonary hypertension. If taken at face value, it does suggest that the vessels have a rigid structure that does not close at low pressures. The data are limited, however, with respect to the number of measurements of pressure and flow, and a rapid fall in flow is likely to occur at pressures lower than we have measured (fig 2b). Consequently, although our data do not support excess vascular closure as a cause of the hypertension in patients with airways obstruction and emphysema, they cannot rule out the possibility that it is important, particularly at

very low vascular pressures.

A true pressure-flow curve for a vascular bed should be plotted as the flow versus the driving pressure for flow—that is, the pressure difference between the entrance and exit from the system. In the pulmonary vasculature this is the pressure difference from the pulmonary artery pressure to the left atrium. There is considerable debate about whether wedge pressure represents an accurate reflection of left atrial pressure in chronic obstructive lung disease. In any case, if the pressure-flow data for the patients with mild to moderate disease and the patients with severe disease are plotted with the difference between pulmonary artery pressure and pulmonary artery wedge pressure representing the driving pressure there is little change in the slopes and intercepts.

The eight patients in this study with severe disease form a subset of a large scale evaluation of oxygen therapy in patients with chronic obstructive lung disease, and the baseline values of the patients reported here are similar to those of the group as a whole.<sup>7</sup> Timms *et al*<sup>7</sup> and Weitzenblum *et al*<sup>17</sup> have showed that continuous oxygen therapy significantly decreased the pulmonary artery pressure, suggesting that hypoxia induced structural changes may be partially reversible. The small arteries have been shown to be the site of hypoxic vasoconstriction,<sup>3</sup> and Reid<sup>4</sup> has shown that the smooth muscle cells respond to hypoxia by constriction. She also emphasises, however, that chronic hypoxia will result in structural changes in these vessels, leading to loss of elasticity, and that these altered vessels are not necessarily more reactive (do not have greater tone) than normal vessels.

Our data are consistent with this hypothesis, showing a significant increase in the percentage of intima and media in the small pulmonary vessels in patients with severe disease. The patients with mild to moderate disease showed an increased intima, but in fact had an overall decrease in the percentage of media. This group had a slight response to oxygen administration, and maybe hypoxic vasoconstriction is a component of mild to moderate disease, the structural changes predominating in severe disease. Hale and coworkers<sup>6</sup> showed a higher percentage of intima and media in patients with airflow obstruction than in non-smokers. Their method differs from ours in that they measured proportions along a perpendicular line and excluded the adventitial components. When we exclude the adventitia compartment, the patients with mild to moderate disease have percentages of media and intima similar to those of the non-smokers.

This study confirms that resting pulmonary artery pressure increases with severity of airflow obstruction, and that this is associated with intimal thickening in

the pulmonary vessels. When the disease is so severe that pulmonary artery pressure is increased at rest, vessels of the same calibre show an increase in the muscular media as well as the intima.

Although the absence of catheterisation data from the group of normal control subjects places constraints on the interpretation of these results, we believe that the conclusions are reasonable. Cardiac catheterisation was not possible in the non-smoking controls, and surgical resection of pulmonary tissue is not feasible in patients with pulmonary hypertension. The comparison of postmortem with surgical material represents an additional potential problem. Both surgical and postmortem material, however, were fixed and processed by the same methods, and we believe that the vascular structures are likely to be similar.

Although this is a cross sectional study, it suggests that early pulmonary arterial changes associated with airflow obstruction consist of intimal proliferation. As the severity of disease increases, pulmonary hypertension on exercise occurs that is sensitive to oxygen administration through a mechanism that is not clear. Sustained pulmonary hypertension, seen in patients with severe disease, is associated with an increase in muscular media as well as intima. These changes are associated with an increased resistance to blood flow that is not sensitive to an increase in the inspired oxygen concentration.

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