Peripheral Airways Obstruction in Idiopathic Pulmonary Artery Hypertension (Primary)*

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The mechanical properties of the lung were studied in ten nonsmokers with idiopathic pulmonary artery hypertension (IPAH) (mean pulmonary artery pressure 65.7 ± 30 mm Hg). In the routine lung test, residual volume was found to be abnormal (>120 percent of the predicted) in seven patients, and measured airway resistance was normal in eight out of the ten patients. A decreased FEF 75-85 percent, abnormal values for the helium-air flow ratios and increased closing capacities were documented in eight of ten patients in whom lung elastic recoil was normal (six of ten) or increased (four of ten). These features suggest peripheral airways obstruction (PAO) which was also supported by histopathologic findings in three cases (one biopsy and two necropsies). The observed changes in lung compliance could be related to the behavior of the coupling of the air-space and vascular compartments. The etiology of PAO in IPAH patients is not known, but our results indicate that both the peripheral airways and the pulmonary circulation are affected. The knowledge of PAO in IPAH patients could help to better understand the observed V/Q inequality in this entity.

Primary or idiopathic pulmonary artery hypertension (IPAH) is a rare entity. A number of theories have been advocated to explain its origin in the absence of concurrent cardiopulmonary disease. Recently, a better understanding of the hemodynamics of this entity and the benefit seen in some patients under vasodilator therapy has helped to explain its pathophysiology. Little is known about pulmonary function tests in IPAH, particularly those concerning lung mechanics. Some have referred to pulmonary function tests as being normal or close to normal. Others have suggested an abnormal diffusing capacity, increased residual volume, and reduced maximum voluntary ventilation. A severe restrictive ventilatory defect in a patient with IPAH that worsened during his clinical course has also been reported.

Our study describes the mechanical properties of the lung in ten patients with IPAH, and shows, in most of them, evidence of peripheral airways obstruction and abnormal lung compliance.

METHODS

The diagnosis of IPAH was made after the exclusion of other known diseases capable of producing pulmonary artery hypertension (PAH), following accepted criteria. There were five male and five female subjects, ranging from 16 to 42 years of age (mean 25 years). At the time of the studies, they had been symptomatic for an average of eight years (range two to 12 years).

All patients presented with a history of dyspnea on exertion. Five patients gave an additional history of syncope. Chest pain on exertion was present in three patients. None had cough or sputum production. All patients had clinical signs of PAH, ECG evidence of right ventricular enlargement, as well as suggestive roentgenographic signs of PAH. Their mean pulmonary artery pressure was 65.7 ± 30 mm Hg, (normal: ±16 mm Hg), the pulmonary arterial resistance was 1165 ± 240 dynes/sec/cm5 (normal: ±100 dynes/sec/cm5), and the pulmonary wedge pressure was normal (6.2 ± 3 mm Hg). The mean cardiac index was 3.0 ± 1.1 L/min/m2.

There were no smokers or obese patients in the group, and none of the women had taken oral contraceptive medication. None of the patients had taken appetite depressant drugs. No patient was included in the study if known to have signs or symptoms of right heart failure, respiratory infection, or history of pulmonary embolism. However, three patients had experienced right cardiac failure and recovered between eight and ten months before the study. None had clinical evidence of air space or restrictive lung disease, and the lung parenchyma was normal roentgenographically in all cases. All patients were permanent residents of México City (altitude 2,240 m).

In all cases, the following laboratory examination results were normal or negative: antinuclear antibodies, lupus erythematosus cells, latex fixation, rheumatoid factor, protein electrophoresis, cryoglobulins, Schirmer test, Ab for Sjögren, pigeons and PPD. A lung biopsy specimen was obtained in one patient (case 7) and necropsy specimens in two (cases 2 and 4). Paraffin sections were done and stained by the hematoxylin-eosin, Masson's trichrome, Ziehl-Nielsen, PAS, and Van Gieson's techniques. All cases examined under the light microscope showed the vascular histopathologic spectrum described in IPAH (Fig 1). All sections were evaluated according to the Heath and Edwards classification of pulmonary hypertensive arterial disease. Two subjects (2 and 7) corresponded to grade 3 (medial hypertrophy, intimal fibrosis and early generalized vascular dilatation, and one (4) to grade 4 (progressive generalized vascular dilatation and occlusion by intimal fibrosis and fibroelastosis, plexiform lesions). Small airways abnormalities were evaluated according to previously reported histologic changes found in patients with these disorders. No cardiac defects in subjects 2 and 4 were demonstrated. Two of the patients were on

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measured in the plethysmograph. Esophageal pressure was used as an index of pleural pressure and was measured by an esophageal balloon (length 10 cm, perimeter 3.5 cm) containing 0.6 ml of air and positioned in the midesophagus. Balloon volume was such that it was relatively independent of balloon pressure, and esophageal pressure was checked for artifacts according to the method of Milic-Emili and co-workers.15 Pressure was also measured at the mouth and transpulmonary pressure was derived as the difference between mouth and esophageal pressures. The flow measurements were made with a Hans-Rudolph heated pneumotachograph and an Statham transducer. All signals were recorded. A marker in front of the patient helped the subject to keep his end-expiratory volume at FRC and his tidal volume (TV) near that of resting TV at various respiratory frequencies.

A constant volume history of inflation to TLC preceded the measurement of Cdyn at each frequency. Maximum expiratory flow volume (MEFV) curves were obtained by plotting flow against volume on the oscillographic photographic recorder. Flow rates from the pneumotachograph were calibrated for air and helium to correct for gases with different viscosity. Several MEFV curves were obtained on air from the seated subject. The patient then inhaled the helium-oxygen mixture (He20 percent-O20 percent) to vital capacity (VC) and then repeated the MEFV maneuvers. The best air and helium MEFV curves were selected.

From the air MEFV curve, flow rates were calculated at 50 percent of the VC (V50 50 percent VC) and 25 percent of the VC (V25 25 percent VC). Flow rates were calculated in liters per second. Results were compared to the normal values of Cherniack and coworkers.16 Zapletal and associates,17 Morris and colleagues,18 and for an altitude of 3,100 m from Kryger and co-workers.19 Due to age limitations, the data reported for high altitude could only be applied to eight of the ten patients (case 4 was 17 years and case 8, 16 years old). Flow rates at 50 percent and 25 percent of VC were also determined on the helium MEFV curves. The flow ratios between the helium and air curves (helium Vxx/air Vxx) at 50 percent and 25 percent of VC were calculated.

Closing capacities were measured by the residual gas (N2) technique.19 Three reproducible curves were obtained in each subject and mean values taken. Each curve was analyzed in terms of the slopes of phase 3, phase 4, and the junction of phase 3 and phase 4. Closing volume was identified as the onset of phase 4 and closing capacity defined as the volume of phase 4 plus RV. Results were

Table I—Pulmonary Function Test in the IPAH Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>PAP mm Hg</th>
<th>TLC†</th>
<th>VC†</th>
<th>FEV/FVC Value†</th>
<th>MMEF Value†</th>
<th>FEF 75-75% Value†</th>
<th>Raw cm H2O/L s/FRC Value†</th>
<th>V50% at VC Value†</th>
<th>V25% at VC Value†</th>
<th>Cst H2O cm L−1 at 90% TLC Value†</th>
<th>Pst (l) cm* H2O at 90% TLC Value†</th>
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<td>82</td>
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Mean ± SD

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<th>7</th>
<th>0</th>
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<th>88</th>
<th>2</th>
<th>4</th>
<th>4</th>
<th>4</th>
<th>7</th>
</tr>
</thead>
</table>

Normal values from references

24, 36, 16, 17, 16, 17, 16, 17, 20, 21, 20, 21, 34, 21, 16, 18, 19, 18, 19, 16, 29

Underlined values represent abnormal results. *Pst (l) is elastic recoil pressure.
†Percent predicted.
‡Values calculated according to Kryger et al. 15
§NS.
¶p<0.001.
* p<0.01.
compared to the normal values of Buist and colleagues. With the patient seated, expired air was collected for three minutes in a Tissot spirometer. Midway through the collection of expired air, blood samples were obtained from the radial artery over a one-minute period (normal values for Mexico City, arterial Pco2 67±5-2.5 mm Hg and arterial Pco2 32.5±2.5 mm Hg⁴⁶,⁴⁸ and immediately analyzed using a gas analyzer (127 bath, 213 electrometer). From these data, the physiologic dead space (using Bohr's equation) and the alveolararterial Pco2 difference (Pa-a] O₂), using the alveolar air equation, were calculated. Normal values for the physiologic dead space are from Harris and co-workers. The methodology for determining the pulmonary shunt calculation (Qs/Qt) has been reported elsewhere and the data presented were obtained during a previous catheterization. Diffusing capacity for CO was not performed as part of the protocol. We tried to correlate our lung function findings with the level of the mean pulmonary artery pressure. Statistical analysis was performed using standard analysis for linear regression and the t-test for independent variables. All results are expressed as mean ± SD.

RESULTS

Pulmonary function data for the IPAH patients are shown in Table 1. The TLC was normal in all patients, and VC was decreased in cases 4 and 5. The RV, measured as thoracic gas volume, was outside the limits of normality in seven out of the ten patients. The FEV/FVC ratio was normal in all patients, the MMEF was decreased in three patients, and the FEF 75-85 percent was abnormal in eight out of the ten patients. When air flow was adjusted for decreased air density at 3,100 m (Mexico City altitude is 2,240 m), the mean average values of the observed MMEF and FEF 75-85 percent for altitude became statistically different when compared to the values calculated according to the regression equations for sea level. The MMEF for sea level is 94±22 percent predicted; MMEF for an altitude of 3,100 m 67±18 percent predicted (p<0.001); FEF, 75-85 percent for sea level = 70±28 percent predicted; for high altitude, 46±14 percent predicted (p<0.01).

Using the regression equation for MMEF at an altitude of 3,100 m, six out of eight patients showed a decreased MMEF. Cases 2 and 7 that showed normal FEF 75-85 percent values, according to the regression equation for high altitude became abnormal. The Raw was found abnormal in two patients (cases 4 and 5). The Vmax 50 percent and Vmax 25 percent was abnormal in four out of the ten patients. Using all these indices (the MMEF, the FEF 75-85 percent, Raw, Vmax 50 percent VC, and the Vmax 25 percent VC), bronchial obstruction was found in nine out of the ten patients. When air flow was adjusted for the air density at high altitude, bronchial obstruction was present in all cases (case 7 showed a MMEF of 70 percent predicted and a FEF 75-85 percent = 73 percent predicted). The Cst was decreased in four patients (cases 1,3,5, and 7), and the elastic recoil pressure at 90 percent of TLC was abnormal in seven patients.

The values for helium-air flow ratios derived from the MEFV curves at 50 percent VC and 25 percent VC, the closing volume, the closing capacity, the slope of phase 3 and the behavior of the Cdyn are shown in Table 2; the helium-air flow ratios at 50 percent VC and 25 percent VC were abnormal in eight out of ten patients.

Abnormal values for closing capacity were found in eight of the ten patients (Fig 2). The alveolar plateau was abnormal in two patients (cases 3 and 5). Frequency dependence of compliance was demonstrated in nine of the ten patients.

Figure 3 shows the static pressure-volume curves obtained during expiration and separated in age groups. The shaded area is the range of normal values given by Turner and co-workers. In six patients, it was found shifted downwards and to the right (cases 1,2,4,5,7, and 8). In two patients (cases 9 and 10), there was a shift upwards and to the left at low lung volume.

Table 2—Helium/Air Flow Ratios, Closing Volume, Closing Capacity, Slope of Phase 3 and Dynamic Compliance in IPAH Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Helium/Air Flow Ratio at 50% VC</th>
<th>Closing Volume (% VC)</th>
<th>Closing Capacity (% TLC)</th>
<th>% N/L</th>
<th>Frequency Dependence of Compliance</th>
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<tbody>
<tr>
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<td>12.5</td>
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<td>139</td>
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<td>0.97</td>
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<tr>
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<tr>
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<td>100</td>
<td>9.3</td>
<td>38</td>
<td>1</td>
<td>D</td>
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<tr>
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<td>106</td>
<td>23.4</td>
<td>60</td>
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<td>19</td>
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<tr>
<td>7</td>
<td>82</td>
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<td>38</td>
<td>1.17</td>
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<tr>
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<td>110</td>
<td>14</td>
<td>25</td>
<td>0.8</td>
<td>D</td>
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<tr>
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<td>0.82</td>
<td>D</td>
</tr>
<tr>
<td>10</td>
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<td>44.8</td>
<td>1.73</td>
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<tr>
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<td>110±16</td>
<td>41.4±9</td>
<td>1.3±0.8</td>
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<td>8</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>9</td>
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*D, demonstrated; ND, not demonstrated. The underlined values represent abnormal results. Normal values are from Buist and co-workers.*
The maximum voluntary ventilation was abnormal (<80 percent predicted) in four patients, and the mean average value for the whole group was 79 ± 18 percent predicted.

Table 3 shows the physiologic dead space, the pulmonary gas exchange, and the anatomic veno-arterial shunt results for the IPAH patients studied. The physiologic dead space-tidal volume ratio (VD/VT) was abnormal in eight patients, and the VD was abnormal in five. The P(A-a)O₂ was increased (>15 mm Hg) in six patients and a decreased PaO₂ (<65 mm Hg) was found in four patients in whom PaCO₂ was in the range of normality for our altitude (30 to 35 mm Hg). The PaCO₂ was below 30 mm Hg in four patients, two of whom showed an abnormal P(A-a)O₂ (case 4 and 9). The Qs/Qt was greater than 5 percent in seven patients. No significant correlation was found between the pulmonary function parameters and the level of the mean pulmonary artery pressure. Necropsy and lung biopsy specimens (cases 2, 4 and 7) showed narrowing of small airways with thickened walls, infiltrated by a great number of lymphocytes, some plasma cells, and a few polymorphonuclear leukocytes (Fig 4). Some airways contained mucus plugs. There were no features suggesting emphysema.

**DISCUSSION**

The patients had most of the features of the entity called idiopathic or primary pulmonary artery hypertension and fulfilled the accepted criteria for the diagnosis. Accordingly, in three patients, the lung biopsy or the necropsy specimens showed the arterial histopathologic spectrum described for IPAH. It has been previously stated that pulmonary mechanical function is close to normal in IPAH patients. However, using lung function tests that detect peripheral airways disease, this concept can no longer be...
Table 3—Physiologic Dead Space, Pulmonary Gas Exchange, and Anatomical Shunt in IPAH Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Vd/Vt ratio</th>
<th>Vd, ml</th>
<th>P (A-s) O₂, mm Hg</th>
<th>PaO₂, mm Hg</th>
<th>PaCO₂, mm Hg</th>
<th>Q̇s/Qt %</th>
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<tr>
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<tr>
<td>Mean ± SD</td>
<td>0.42 ± 0.10</td>
<td>177 ± 59</td>
<td>16 ± 6</td>
<td>67 ± 8</td>
<td>29 ± 2</td>
<td>7 ± 4</td>
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</tbody>
</table>

No. patients outside of limits of normality
Normal values from references

| 8 | 5 | 6 | 4 | 4 | 7 |

Supported. Our patients were nonsmokers, and no other cause of airway disease was identified. Therefore, the abnormalities seen were most likely related to IPAH. Normal forced exhaled flow rates may be preserved in the presence of significant peripheral airways obstruction. If tests to detect such peripheral airways abnormalities had not been performed, only three of our patients would have shown an increased airways resistance as measured by the observed MMEF and Raw values (cases 4, 5, and 10). Also, such abnormalities could only explain the abnormal increase in RV documented in three of the seven patients.

When MMEF values are adjusted for air density at high altitude, two additional patients showed an abnormality (case 1 and 6) that could explain the increase in RV. A measurement of FEF 75-85 percent lower than 75 percent of the predicted value is capable of identifying subjects with small airways disease. In the present study, this index was abnormal in eight patients, three of whom had a normal MMEF with an increased RV (case 1, 3, and 6). With the indices derived from the flow-volume curves with air, it could only be possible to detect abnormalities in exhaled flow rates in four patients in whom the MMEF and FEF 75-85 percent were abnormal.

The habitat of the studied population was 2,240 m and the predicted normal values used to detect airways obstruction were taken from sea level studies and also from the FEV/FVC, MMEF, and FEF 75-85 percent reported at a higher altitude of 3,100 m. The latter data were considered because, although flow limitation may not be apparent in airways in which flow is turbulent, the diminished air density at a higher altitude could underestimate an abnormal resistance to air flow.

Using flow-volume curves with He-O₂, an increased resistance to air flow in the peripheral airways was found in eight of the cases studied. On the other hand, the closing volume and the closing capacity were also abnormal in eight cases.

As far as we know, there is no evidence that values obtained from the flow-volume curves with He-O₂ or from indices derived from the single breath nitrogen curves might be different at our altitude relative to those obtained at sea level.

Flow rates may be reduced solely by loss of elasticity, and the airways themselves may appear structurally normal. None of the IPAH patients studied showed a loss of elasticity. In fact, in four, the elastic recoil was increased. The abnormal figures recorded for the MMEF curves, for the FEF 75-85 percent, for the V̇eff 50 percent VC and V̇eff 25 percent VC (with air), for the CV/VC, for the closing capacity in the absence of loss of elastic recoil, and in the presence of close to normal Raw measurements, represent abnormalities that reflect peripheral airways obstruction in

Figure 4. Small airways infiltrated by a great number of lymphocytes, some plasma cells, and a few polymorphonuclear leukocytes (hematoxylin-eosin, original magnification × 256).
the IPAH patients. An increase in flow at 50 percent of VC when breathing He-O₂ was observed in eight of the patients. This is independent of lung elastic recoil, and thus, may be more specific for detecting abnormality in peripheral airways.

These findings in IPAH patients support the idea that the caliber of the small airways is reduced. This feature could explain the increase in RV observed in this entity. Our findings are also supported by the pathologic observations in the three cases studied that showed small airways disease.

The observed changes in lung compliance and elastic recoil in IPAH cannot be attributed to a reduction in the number of air spaces (ie, pulmonary fibrosis). It is, however, possible that such changes might be the result of the pathologic changes present in the pulmonary vasculature. As has been proposed previously by our group, and by other investigators, it could be the result of perivascular and vascular thickening which may render the air-vessel space less distensible.

Clearly, the real explanation for the observed changes in lung compliance and elastic recoil remain speculative.

It has been observed that arterial oxygen saturation decreases with progression of the disease and that hypoxemia and/or widened P(A-a)O₂ is caused mainly by V/Q inequality and low mixed venous oxygen content without evidence of a diffusion impairment. In some cases, it is also due to an intracardiac shunt secondary to a patent foramen ovale. The development of hypoxemia and the increased ratio of dead space to TV observed in some of our patients in the absence of evidence suggesting alveolar destruction, also suggest abnormalities of ventilation distribution. Also Vd/VT changes could result from the vascular abnormality causing a decrease in perfusion with secondary increase in airways resistance to flow in nonperfused areas. The anatomic lesions of IPAH primarily cause a restriction of the pulmonary vascular bed that results in maldistribution of the pulmonary blood flow. On the other hand, as a result of abnormalities in the peripheral airways with secondary maldistribution of alveolar ventilation, a ventilation-blood flow imbalance ensues. The knowledge of the peripheral airways obstruction that occurs in IPAH patients could help to better understand the impairment in gas exchange when present in this entity. The results from this study indicate that in IPAH, besides the pulmonary microcirculation, the peripheral airways are affected. In considering the relation of vascular and airway disease, we cannot, however, distinguish between cause/effect or independent processes.

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ACCP Course: Review in Critical Care Medicine

The American College of Chest Physicians will present this board review course at the Hyatt Regency Hotel, Chicago, June 13-17, under the direction of Drs. Roger C. Bone, David R. Dantzker and Thomas L. Petty.

The systematic approach to the critically ill patient saves many lives each year. The conceptual and technologic evolution of the field of critical care medicine has demanded a frequent update in knowledge for many physicians involved in the day-to-day care of desperately ill patients. Thus, the American College of Chest Physicians has organized this in-depth and timely review for anesthesiologists, cardiologists, internists, pediatricians, pulmonologists and surgeons. This course is especially designed for physicians who are preparing for the upcoming certification examination in critical care. An outstanding faculty, all experts in critical care medicine, will provide a thorough review of established and new methods and approaches to patients suffering all forms of major organ system failure.

An interactive computer system will be used throughout the course. This system will allow the registrants to react to each presentation via hand held keypads. The computer system will immediately sum up the results from all voting stations and present them on a color bar chart, through a video projector. Registrants will see how they compared with their peers, and know if they were right or wrong. All scores will be kept confidential and, at the end of the course, a computer printout with individual scores and class averages for each content area will be available.

Upon registration for this meeting, attendees will receive additional directions and study material.