Reversal of Pulmonary Hypertension by Prolonged Oxygen Administration to Patients with Chronic Bronchitis

By Abraham S. Abraham, M.B., Richard B. Cole, M.D., and John M. Bishop, D.S.C., M.D.

ABSTRACT
Established pulmonary hypertension associated with hypoxemia in patients with chronic bronchitis is probably secondary to hyperplasia of the smooth muscle of pulmonary arterioles. To investigate the possibility that this increase in pulmonary arterial pressure was reversible, the floating catheter technique was used to study the effects of continuous administration of oxygen for 4 to 8 weeks on the pulmonary circulation.

In six patients, there was a gradual fall in pulmonary arterial pressure, the mean pressure for the group being 42.5 mm Hg before, and 32.3 mm Hg after, the period of oxygen administration. All measurements were made when the patients breathed air. There was no change in cardiac output. Hematocrit decreased from 51.4% to 42.5%, but total blood volume remained unchanged.

It has been shown previously that brief inhalation of oxygen can cause a slight temporary reduction in the pulmonary hypertension associated with chronic bronchitis and anoxemia. The present findings show that the residual, established hypertension is also reversible if oxygen therapy is continued for weeks. It is suggested that this reversal may be brought about by regression of the muscular hyperplasia of the small pulmonary vessels consequent to long-term relief of hypoxia.

ADDITIONAL KEY WORDS
muscular hyperplasia of pulmonary arterioles
pulmonary vascular resistance
floating catheter
chronic alveolar hypoxia

Patients with chronic bronchitis often have pulmonary hypertension. During an episode of acute respiratory failure, a further increase in pulmonary arterial pressure is seen. Treatment of such an exacerbation of the disease will reverse the acute rise in pulmonary arterial pressure (1-4). Nevertheless, following treatment a certain degree of pulmonary hypertension and arterial unsaturation will persist in some patients. Correction of this hypoxia by the acute administration of 100% oxygen has been shown to produce only a small fall in pulmonary arterial pressure, which is reversed when the oxygen administration is discontinued (5, 6). These observations do not account for the underlying persistent pulmonary hypertension which has hitherto been attributed to irreversible changes in the pulmonary vascular bed.

Histological examination of the lungs of patients dying with chronic bronchitis and right ventricular hypertrophy has shown that the characteristic vascular change is muscular hyperplasia of the pulmonary arterioles (7).

It seemed possible that pulmonary hypertension in such patients might be due to the muscular hyperplasia which itself resulted from persistent vasoconstriction due to chronic alveolar hypoxia. If this hypothesis were true, prolonged relief of alveolar hypoxia might reduce the degree of pulmonary hypertension by...
The six men studied had chronic bronchitis (8) for 20 to 35 years, and all gave a history of episodes of congestive failure in the past. All were disabled by the disease and had been unable to work for some years. The patients' ages, heights, and weights are given in Table 1. Five of them had been seen at regular intervals during the previous 1 or 2 years and had undergone cardiac catheterization. There was no history of recent chest infection or clinical deterioration. After the first week of investigations was completed, the patient was interviewed again and consent obtained to continue the study. The studies were started and largely completed during the summer of 1967.

**Methods**

The six men studied had had chronic bronchitis (8) for 20 to 35 years, and all gave a history of episodes of congestive failure in the past. All were disabled by the disease and had been unable to work for some years. The patients' ages, heights, and weights are given in Table 1. Five of them had been seen at regular intervals during the previous 1 or 2 years and had undergone cardiac catheterization. There was no history of recent chest infection or clinical deterioration. After the first week of investigations was completed, the patient was interviewed again and consent obtained to continue the study. The studies were started and largely completed during the summer of 1967.
LONG-TERM OXYGEN AND PULMONARY HYPERTENSION

TECHNICAL METHODS

Arterial pressure was measured through a polythene catheter inserted into a brachial artery by the Seldinger technique. A 19-gauge needle and cannula was inserted into an antecubital vein, and a flexible nylon catheter (i.d. 0.75 mm, o.d. 0.94 mm) was introduced through the cannula and "floated" into a branch of the pulmonary artery. The position of the tip was continuously determined by the form of the recorded pressure wave. Previous trials have shown that tracings obtained in this way were identical to those obtained simultaneously from a no. 9 double lumen Courmand catheter (Fig. 1). In 15 out of 46 studies, a pulmonary wedge tracing was also obtained at the beginning of the study (Fig. 2). The catheter was then withdrawn into the pulmonary artery, and pulmonary arterial pressure and cardiac output were measured so that pulmonary vascular resistance could be calculated (9). The pulmonary arterial catheter was usually inserted into the same vein and site on several occasions; the number in each patient is evident from Figure 3. Each study was carried out at the same time of day and took about an hour to complete; both catheters were then removed. During the study, the venous catheter was kept patent with an infusion of normal saline containing 1 unit of heparin/ml; not more than 100 ml was infused during the entire study.

![Figure 2: Tracing obtained on withdrawing the floating catheter into the pulmonary artery from a pulmonary wedge position.](image1)

![Figure 3: The changes in pulmonary arterial pressure, cardiac output and pulmonary vascular resistance during the control period, period of oxygen administration (shaded) and after stopping oxygen. All measurements made with the patient breathing air for two hours.](image2)
arterial catheter was flushed periodically with 2 to 3 ml of a similar solution. No problem with clotting was encountered, no catheter needed replacing during a study, and no adverse effects or complications were observed.

Intravascular pressures were recorded by a transducer employing the differential transformer principle (S.E. Laboratories Type 267 B) and recorded on an ultraviolet photographic recorder. The patient was semirecumbent and the zero reference point was the level of the mid right atrium. Mean pressures were determined by planimetry over several respiratory cycles.

Cardiac output was measured by the dye dilution method (10), 2.5 mg of indocyanine green being injected into the pulmonary artery. Blood, withdrawn continuously from the brachial artery, was passed through a densitometer (Gilford Inst. Lab. Inc. Model 103 IR) and later returned to the patient. The primary curve was obtained by semilogarithmic correction and its area determined by planimetry.

Microelectrodes (Radiometer) were used for measurement of arterial oxygen and carbon dioxide tensions and pH. The standard bicarbonate was obtained from a nomogram (11). Arterial and mixed venous percent oxygen saturations were obtained spectrophotometrically.

Plasma volume was measured using 125I-labeled human albumin; 1 to 2 μc of 125I was injected on each occasion. Plasma volume calculations were based on zero time counts obtained by extrapolation of semilogarithmic plots of plasma 125I counts 30, 45, and 60 minutes after injection. 51Cr and 125I activities were counted to 1% accuracy in the same samples of arterial whole blood, or standards, using a well-type scintillation counter and pulse height and analyzer. Blank counts before injection gave residual 51Cr and 125I activity prior to the next measurement.

Arterial hematocrits were read in Wintrobe tubes after centrifugation at 2000 × g for 30 minutes, using a factor of 0.98 to correct for trapped intercellular plasma (14).

CLINICAL PROCEDURE

Patients were admitted to hospital some days before the study was started. During this initial period, there was no evidence of any change in the patients' clinical state, and their weight remained steady. Treatment, which included breathing exercises and postural drainage, bronchodilators, and diuretics, was continued throughout the stay in hospital.

For the first week of the study the patient wore a nasal catheter connected to an oxygen cylinder which he could push around on a trolley. However, a large hole had been cut in the catheter so that the patient breathed air, as confirmed by random measurements of arterial blood gas tensions. At the end of the week (and in patients A.G. and P.H. at the end of 2 and 4 weeks, respectively), the defective catheter was replaced without the patient's knowledge.

Oxygen was now administered at 2 liters/min to four patients, and 1 liter/min and 3 liters/min to the other two patients, corresponding to an inspired oxygen concentration of 31%, 27%, and about 34% respectively (15). Random measurements of arterial blood gas tensions (Table 2) showed that this raised the arterial oxygen tension (Pao2) to an average of 74.5 mm Hg in the six patients (range, 63 to 94 mm Hg), while the
arterial carbon dioxide tension \((P_{aCO_2})\) varied from 58 to 99 mm Hg, with an average of 71.6 mm Hg. This compared with initial values when breathing air of \(P_{aO_2}\) 55.4 mm Hg (range, 43 to 62 mm Hg) and \(P_{aCO_2}\) 64.6 mm Hg (range, 35 to 73 mm Hg).

At the end of 4 to 8 weeks, the defective nasal catheter was reintroduced so that the patient was now, again unknowingly, breathing air. At the end of this period (3 to 6 weeks), the patient was discharged. Three weeks later he was readmitted for final measurements.

Each complete study at each phase consisted of the following measurements, all of which were carried out with the patient breathing air for at least 2 hours.

1. Exercise tolerance determined by recording the distance the patient could walk on a treadmill at a fixed rate before having to stop because of dyspnea.

2. Oxygen uptake at rest and during exercise.


4. Intravascular pressures and cardiac output measured twice, the two measurements being separated by about 3 minutes, during which arterial and mixed venous blood was taken for estimation of \(P_{aO_2}\), \(P_{aCO_2}\), and percent \(O_2\) saturation. Mean results of each of these pairs of readings were used for calculations. Measurements were made with the patient lying in bed after he had breathed room air for at least 3 hours, and again after breathing oxygen at 1 to 3 liters/min for 30 minutes. For each patient the rate of oxygen delivery was the same as that previously given.

5. Arterial hematocrit was measured weekly. Blood volumes were measured at the beginning and end of the control period, and again at the end of the period of long-term oxygen administration.

Results

The results of lung function tests are given in Table 1. Values for pulmonary arterial pressure, cardiac output and arterial blood gas tensions before, during and after long-term treatment with oxygen are in Table 3, and values for blood volumes in Table 4. The \(t\)-test was applied to the individual differences between the values obtained during the control and end of the oxygen-breathing periods.

CONTROL PERIOD BEFORE OXYGEN THERAPY

No significant changes were observed during the control period in any of the measured variables except exercise tolerance, which increased in four patients. All patients had pulmonary arterial hypertension (range in mean pressure, 29 to 57 mm Hg). Pulmonary wedge pressure, measured in four patients, ranged from 7 to 14 mm Hg. The range of pulmonary vascular resistance in these patients was calculated to be 427 to 618 dyne·sec·cm\(^{-5}\). Cardiac output ranged from 3.44 to 4.18 liters/min. All of the patients had arterial hypoxemia and hypercapnia.

PERIOD OF OXYGEN THERAPY

Oxygen was discontinued about 2 hours before the measurements during this period were made, and the patient breathed air. Pulmonary arterial pressure fell in each patient; the average fall in mean pressure was 10.2 mm Hg (from 42.5 to 32.3 mm Hg; \(P < 0.01\)).

In five patients, the time course of this change was obtained (Fig. 3). In four patients a decrease was noted at the end of the first week, and in three of these, the fall continued throughout the period of study. One patient (P.H.) had an initial rise in pulmonary arterial mean pressure, which was first measured at the end of a fortnight on oxygen, but this was associated with a marked decrease in \(P_{aO_2}\). Subsequently, however, although \(P_{aO_2}\) remained low, the pulmonary arterial pressure fell and 3 weeks later was lower than during the control period. Pulmonary wedge pressure, measured in four patients before and during oxygen therapy, showed no change; in three of these four, pulmonary vascular resistance decreased.

The mean cardiac output increased to 4.28 liters/min but the change was not significant, and there was no change in oxygen uptake or A-V oxygen difference. The \(P_{aCO_2}\) fell in four of the six patients, when breathing air, tending to return toward control values by the end of this period. The \(P_{aCO_2}\) of five of the six patients, breathing air, was also lower than in the control period. Arterial pH increased in all patients during the period of oxygen therapy,
TABLE 3

Pulmonary Arterial Pressure, Cardiac Output, Pulmonary Vascular Resistance, Blood Gas Tensions and Acid Base State

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pulmonary Arterial Pressure (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Pulm. vase. resist (dyno/sec/cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>J.L.</td>
<td>42</td>
<td>34</td>
<td>3.44</td>
</tr>
<tr>
<td>P.H.</td>
<td>32</td>
<td>33</td>
<td>4.15</td>
</tr>
<tr>
<td>F.P.</td>
<td>39</td>
<td>32</td>
<td>4.99</td>
</tr>
<tr>
<td>A.C.</td>
<td>57</td>
<td>48</td>
<td>3.96</td>
</tr>
<tr>
<td>F.S.</td>
<td>56</td>
<td>54</td>
<td>4.18</td>
</tr>
<tr>
<td>S.R.</td>
<td>29</td>
<td>37</td>
<td>3.49</td>
</tr>
<tr>
<td>MEAN</td>
<td>42.5</td>
<td>36.0</td>
<td>3.87</td>
</tr>
</tbody>
</table>

I, Control period; II, End of long-term oxygen, patient breathing air; III, Three weeks after stopping oxygen.

TABLE 4

Blood Volume Measurements

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hct</th>
<th>Red cell vol. (L)</th>
<th>Plasma vol. (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>J.L.</td>
<td>52.8</td>
<td>40.3</td>
<td>41.8</td>
</tr>
<tr>
<td>P.H.</td>
<td>45.7</td>
<td>41.3</td>
<td>42.2</td>
</tr>
<tr>
<td>F.P.</td>
<td>64.8</td>
<td>51.4</td>
<td>54.2</td>
</tr>
<tr>
<td>A.C.</td>
<td>53.3</td>
<td>46.6</td>
<td>44.2</td>
</tr>
<tr>
<td>F.S.</td>
<td>47.2</td>
<td>38.6</td>
<td>37.9</td>
</tr>
<tr>
<td>S.R.</td>
<td>44.7</td>
<td>39.4</td>
<td>37.9</td>
</tr>
<tr>
<td>MEAN</td>
<td>51.4</td>
<td>42.5</td>
<td>44.1</td>
</tr>
</tbody>
</table>

I, Control period; II, End of long-term oxygen; III, Three weeks after stopping oxygen.

and standard bicarbonate concentration also rose.

The arterial hematocrit showed a serial fall in all patients; the mean change from control to end of oxygen therapy periods was from 51.4% to 42.5% (P<0.01). The average red cell volume decreased from 2.2 liters to 1.7 liters (P<0.05), and the plasma volume increased from 2.2 liters to 2.6 liters (P<0.001). Total blood volume fell in one patient from 5.2 to 4.6 liters, but the mean total blood volume for the six patients remained unchanged at 4.4 liters (Fig. 4).

Exercise tolerance increased remarkably in all patients during their stay in hospital, even though there was no specific program of training. However, the increase occurred before oxygen therapy was started in four patients and there did not appear to be any difference in magnitude before and during oxygen therapy. No consistent change occurred in static lung volumes or 1-second forced expiratory volume, throughout the patients’ stay in hospital.

CONTROL PERIOD AFTER OXYGEN THERAPY

The time during which observations were made after oxygen therapy had finished varied from 3 to 6 weeks. During this time, the pulmonary arterial pressure rose in all five of the patients in whom it was measured; the average rise was from 29 to 36 mm Hg 3 weeks after the end of oxygen therapy. Cardiac output remained unaltered and pulmonary vascular resistance rose in the two patients in whom it was measured.

The changes in arterial oxygen and carbon dioxide tensions showed no consistent pattern during this period. Arterial hematocrit had risen in four of the five patients studied 3 weeks after the finish of oxygen therapy. The improvement in exercise tolerance noted before and during oxygen therapy was generally maintained.

Blood Volume Measurements
EFFECTS OF THE ACUTE ADMINISTRATION OF OXYGEN

Oxygen in the concentration used during the period of oxygen therapy was given for 30 minutes on the occasion of each study both during the preliminary control period and during the period of oxygen therapy.

The mean results before and during the oxygen therapy periods for each patient are shown in Figure 5. The average pulmonary arterial mean pressure fell from 43 to 40 mm Hg and from 36 to 34 mm Hg, respectively. During the control period oxygen inhaled briefly did not reduce the pulmonary arterial mean pressure in any patient to the level finally reached after long-term oxygen therapy.

$P_{aO_2}$ rose during the acute administration of oxygen from a mean of 54.8 to 89.4 mm Hg in the control period and from 51.0 to 103.7 mm Hg during the phase of oxygen therapy. During the same periods, the mean $P_{aco_2}$ rose from 66.3 to 67.7 mm Hg and from 66.1 to 71.0 mm Hg, respectively while the arterial pH fell from 7.345 to 7.336 units and from 7.406 to 7.371 units, respectively. These differences were not statistically significant.

Discussion

In all patients pulmonary arterial pressure fell during the period of continuous administration of oxygen. Since pulmonary arterial pressure rises during acute respiratory failure with fluid retention, the first possibility which must be considered is whether these patients were recovering from such an episode. Care was taken to ensure that this was not the

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**FIGURE 4**

Effects of prolonged oxygen administration in six patients. Values are means for the control period (air) and at the end of the period of prolonged oxygen administration ($O_2$). All measurements were made while the patients breathed room air.
case by a careful clinical evaluation before, during, and after the investigation. Furthermore the studies were performed during summer when the patients were free from respiratory infection and in their usual state of health.

There is no evidence that treatment in the hospital, in itself, was responsible for the observed change, since pulmonary arterial pressure did not change during the 1- to 4-week preliminary control period. In addition, it returned toward its initial high values when oxygen administration was discontinued, both before and after the patients were discharged from the ward. Nevertheless, it is necessary to consider whether any of the ancillary methods of treatment given to the patients could have been responsible for the changes in pulmonary arterial pressure. It seemed possible that regular physiotherapy coupled with bronchodilator and effective diuretic treatment might increase alveolar ventilation and so reduce pulmonary arterial pressure, but no systematic change was observed in the patients' lung volumes or respiratory flow rates and no improvement was seen in the distribution of ventilation measured by the single-breath O₂ test. In addition, arterial O₂ saturation values (patients breathing air), which might be expected to increase with improvement in alveolar ventilation, did not change systematically, and no patient had a weight loss, which might indicate that a significant diuresis had occurred. This evidence suggests that the therapeutic effects of admission to the hospital did not in themselves bring about the reduction in pulmonary arterial pressure and that some other factor must account for it.

There was no change in cardiac output, so this factor may be eliminated as a cause for the decreased pulmonary arterial pressure. The hematocrit decreased during oxygen therapy to an extent similar to that observed by Chamberlain and Millard (17). The associated reduction in blood viscosity is unlikely to have influenced pulmonary arterial pressure, since Segel and Bishop (18) found no such change with larger reductions of blood viscosity in a group of similar patients, unless there was also a reduction in total blood volume. There was no such change in total blood volume during the present study.

While the patients breathed oxygen during the period of oxygen therapy, the PacO₂ rose to a variable extent, and there was an associated rise in standard bicarbonate. When the patient had breathed air for 2 hours, the PacO₂ had fallen, presumably because of the increased hypoxic stimulation to ventilation, and arterial pH had consequently risen above control values. Enson et al. (19) observed that an induced acute rise in pH causes a fall in pulmonary arterial pressure, although others have not been convinced of any effect (20, 21). Furthermore, in the present studies, the observed fall in pulmonary arterial pressure was associated with a rise in pH only when the measurements were made while the patients breathed room air; a further fall in pulmonary arterial pressure was observed when the patients breathed oxygen but this was associated with a marked fall in pH. It therefore seems unlikely that changes

![Graph showing mean results in each patient of breathing oxygen for 30 minutes during the control studies (air period) and during the weeks of oxygen administration (oxygen period).](http://circres.ahajournals.org/)

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in pH caused the observed changes in pulmonary arterial pressure.

It is concluded that the observed decrease in pulmonary arterial pressure and pulmonary vascular resistance when breathing air must have been due to an increase in caliber of the pulmonary resistance vessels, that is, presumably the pulmonary arterioles according to the classification of Brenner (22). Hicken et al. (7) described characteristic histologic changes in these vessels in patients with chronic bronchitis and emphysema and evidence of pulmonary hypertension and right ventricular hypertrophy. One of these changes is a circular layer of smooth muscle in the media of the pulmonary arterioles, with little or no hyperplasia of the circular smooth muscle of the small muscular pulmonary arteries. Both classes of vessel also have layers of longitudinal smooth muscle internal to the internal elastic lamina, but do not have the internal fibrosis characteristic of other disorders associated with pulmonary hypertension, such as mitral stenosis. From their histologic structure, therefore, these lesions appear to be potentially reversible. Very similar histologic changes are found in other conditions associated with chronic hypoxia, including the effects in healthy men of living at high altitude (23), patients with chronic mountain sickness (Monge's disease), and patients with severe kyphoscoliosis or gross obesity with alveolar underventilation (24).

A number of studies have shown that the pulmonary hypertension of high altitude is reversible by descent to lower altitudes. In 11 subjects with a mean pulmonary arterial pressure of 24 mm Hg at 14,200 feet, the mean pulmonary arterial pressure decreased to 12 mm Hg after 2 years at sea level (25). A similar study by Grover et al. (28) concerned a 15-year-old girl whose mean pulmonary arterial pressure fell from a resting level of 44 mm Hg, at 10,200 feet to 17 mm Hg, 11 months after she had been brought down to sea level. Similar changes in pulmonary arterial pressure with altitude have been demonstrated in calves (27, 28). Alexander et al. (29), in a study of cattle with high mountain disease, found both a significant fall in pulmonary arterial pressure and a reduction of the medial muscle mass in the small pulmonary arteries and arterioles 12 to 14 weeks after the cattle were brought down to low altitudes.

There is a little presumptive evidence that a similar resolution of the structural changes may also occur in patients with extreme obesity when weight is reduced (30); also in a patient with gross kyphoscoliosis, pulmonary arterial pressure fell after prolonged assisted ventilation (31).

The present observations suggest that regression of the structural changes in the pulmonary arterioles occurred during the course of prolonged correction of the hypoxia, resulting in a fall in pulmonary arterial pressure and pulmonary vascular resistance. Since this study was begun, the results of a somewhat similar investigation have been published (32). These authors found a fall in pulmonary arterial pressure in three out of six patients, and a reduction in pulmonary vascular resistance in four.

The present findings make it probable that the structural changes in the pulmonary arterioles which lead to pulmonary hypertension in patients with chronic bronchitis are due to an hypoxic environment around these vessels. It is therefore of interest to ask why only some patients with chronic bronchitis or with emphysema develop these changes, while other patients equally disabled and with equally severe airways obstruction have a normal pulmonary arterial pressure. The answer seems likely to lie in a better understanding of the detailed spatial relationships between the kind of blood vessel affected and the air spaces, and of the ventilation of these air spaces and the consequent gas tensions within them.

We have insufficient information to judge the possible therapeutic value of prolonged oxygen therapy in such patients. It might, however, be possible to prevent the recurrence of congestive failure if a sustained reduction in pulmonary hypertension could be achieved, and further exploration of this possibility seems worth while. The improve-
ment in exercise tolerance during the course of these studies was striking, but it cannot be attributed to the oxygen therapy, and no specific course of training was given to the patients. We are therefore at present unable to give a physiological explanation for this improvement.

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References

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