Effects of Acute Hypoxia and Exercise on the Pulmonary Circulation

By Alfred P. Fishman, M.D., Harry W. Fritts, Jr., M.D., and André Cournand, M.D.

Two major obstacles complicate the study of the pulmonary circulation in man: the inaccessibility of the pulmonary vessels for direct cannulation, and the multiplicity of extravascular factors that influence pressure-flow-volume relationships within the lungs. New technics have largely circumvented the first difficulty; the second difficulty is minimal in the normal resting subject, but is exaggerated by either physiologic stress, e.g., exercise, or by abnormalities of the heart or lungs.

Observations on a variety of experimental preparations have afforded considerable insight into the regulation of the pulmonary circulation. Particularly rewarding have been the demonstrations by Beyne in the dog and by von Euler and Liljestrand in the cat, that acute hypoxia, hypercapnia, or both elicit pulmonary hypertension. These observations constitute a landmark in studies of the regulation of the pulmonary circulation since they afforded an experimental tool for the production of a pulmonary pressor response, and provided a hypothesis, which could be tested, concerning the adaptation of pulmonary capillary perfusion to alveolar ventilation. Others have subsequently reproduced the pressor response to acute hypoxia in animals and in man, attempts to reproduce the pulmonary pressor response to acute hypercapnia have yielded far less consistent results.

The present studies were designed to elucidate some of the mechanisms involved in the pulmonary vascular responses of man to acute hypoxia and to acute hypercapnia. This first report compares the effects of acute hypoxia and of exercise on pressure-flow relationships in normal subjects, in patients with restricted vascular beds, and in a patient with sympathetic denervation of the lungs. The second paper, because of the special technics involved, is confined to the effects of acute hypoxia on the pulmonary blood volume. The third considers the effects of acute hypercapnia on pressure-flow relationships in the pulmonary circulation.

Methods

All patients underwent a preliminary period of adjustment to the laboratory, its personnel, and facsimiles of the experimental protocol; this consisted of trial runs on a variety of hypoxic breathing mixtures coupled with collections of arterial blood and expired gas. Those who tolerated these procedures well subsequently served as experimental subjects.

All tests were performed in the postabsorptive state, without medication. Venous catheterization of the right heart was performed in the usual manner and the tip of the catheter was placed in the pulmonary artery. The combination of the right heart catheterization, arterial cannulation, and the open-circuit method for collection of expired gas supplied the samples necessary for the calculation of the oxygen uptake (VO2), the respiratory exchange ratio (RER), and the cardiac output (Q) by application of the Fick principle. For the recording of pulmonary and systemic arterial pressures, Statham gages were used as pressure transducers, in conjunction with high-sensitivity carrier amplifiers and photographic registration of the cathode-ray images.

The protocols were designed to satisfy criteria for the "steady state." In brief, these criteria consist of clinical evidence for stability of the respiration and circulation at each level of oxygenation, supplemented by the objective evidence (in the form of RER, VO2) for the equality of gas exchange measured at the mouth to that occurring.
Table 1  
Changes in Ventilation and Gas Exchange during Acute Hypoxia in Ten Normal Subjects  

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Breathing mixture: Ambient air</th>
<th>Breathing mixture: 12-14% O\textsubscript{2} in N\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.S.</td>
<td>35</td>
<td>M</td>
<td>(\dot{V}_E\text{ min.} / M^2)</td>
<td>(\dot{V}_{O_2}\text{ ml/min.} / M^2)</td>
</tr>
<tr>
<td>A.P.</td>
<td>48</td>
<td>M</td>
<td>1.77</td>
<td>4.27, 138, .85, 5.26, 147, .90</td>
</tr>
<tr>
<td>W.M.</td>
<td>49</td>
<td>M</td>
<td>1.76</td>
<td>5.73, 136, .92, 7.04, 147, .94</td>
</tr>
<tr>
<td>H.P.</td>
<td>44</td>
<td>F</td>
<td>1.56</td>
<td>4.61, 125, .81, 5.64, 129, .90</td>
</tr>
<tr>
<td>H.M.</td>
<td>35</td>
<td>M</td>
<td>2.10</td>
<td>3.38, 118, .88, 4.12, 127, .98</td>
</tr>
<tr>
<td>G.H.</td>
<td>35</td>
<td>F</td>
<td>1.54</td>
<td>4.25, 140, .84, 5.96, 147, .94</td>
</tr>
<tr>
<td>E.J.</td>
<td>68</td>
<td>M</td>
<td>1.58</td>
<td>4.51, 131, .86, 5.03, 132, .91</td>
</tr>
<tr>
<td>C.D.</td>
<td>51</td>
<td>M</td>
<td>1.71</td>
<td>4.20, 104, .85, 4.69, 108, .91</td>
</tr>
<tr>
<td>B.J.</td>
<td>25</td>
<td>M</td>
<td>1.88</td>
<td>4.18, 147, .84, 4.61, 148, .93</td>
</tr>
<tr>
<td>F.D.</td>
<td>48</td>
<td>M</td>
<td>1.80</td>
<td>4.96, 124, .94, 6.51, 149, 1.04</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td>4.52</td>
<td>129, .87, 5.51, 137, .92</td>
</tr>
</tbody>
</table>

\(\dot{V}_E\), minute ventilation; \(\dot{V}_{O_2}\), oxygen uptake; \(R_e\), respiratory exchange ratio.

Table 2  
Changes in Arterial Blood Oxyhemoglobin Saturation, Cardiac Output, Pulmonary and Systemic Artery Blood Pressures during Acute Hypoxia in Ten Normal Subjects  

<table>
<thead>
<tr>
<th>Subject</th>
<th>Arterial blood O\textsubscript{2} sat., %</th>
<th>Cardiac output, L/min./M\textsuperscript{2}</th>
<th>Heart rate, per min.</th>
<th>Pulmonary artery (P_a) mm. Hg</th>
<th>Brachial artery (P_a) mm. Hg</th>
<th>Breathing mixture: Ambient air</th>
<th>Breathing mixture: 12-14 O\textsubscript{2} % in N\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.S.</td>
<td>98</td>
<td>4.62</td>
<td>88</td>
<td>21/9, 15</td>
<td>130/79, 99</td>
<td>66</td>
<td>5.26</td>
</tr>
<tr>
<td>A.P.</td>
<td>95</td>
<td>3.26</td>
<td>83</td>
<td>12/6, 9</td>
<td>144/76, 105</td>
<td>70</td>
<td>3.68</td>
</tr>
<tr>
<td>W.M.</td>
<td>96</td>
<td>3.41</td>
<td>83</td>
<td>28/11, 18</td>
<td>122/78, 98</td>
<td>74</td>
<td>4.87</td>
</tr>
<tr>
<td>H.P.</td>
<td>95</td>
<td>2.86</td>
<td>80</td>
<td>22/11, 16</td>
<td>125/68, 98</td>
<td>76</td>
<td>3.22</td>
</tr>
<tr>
<td>H.M.</td>
<td>98</td>
<td>2.63</td>
<td>67</td>
<td>27/11, 18</td>
<td>--</td>
<td>73</td>
<td>3.43</td>
</tr>
<tr>
<td>G.H.</td>
<td>98</td>
<td>3.88</td>
<td>82</td>
<td>13/7, 10</td>
<td>122/78, 98</td>
<td>84</td>
<td>4.08</td>
</tr>
<tr>
<td>E.J.</td>
<td>95</td>
<td>4.30</td>
<td>80</td>
<td>16/6, 11</td>
<td>153/79, 109</td>
<td>85</td>
<td>4.68</td>
</tr>
<tr>
<td>C.D.</td>
<td>95</td>
<td>2.78</td>
<td>73</td>
<td>18/9, 13</td>
<td>132/79, 102</td>
<td>86</td>
<td>4.01</td>
</tr>
<tr>
<td>B.J.</td>
<td>98</td>
<td>3.43</td>
<td>78</td>
<td>20/10, 14</td>
<td>125/68, 86</td>
<td>87</td>
<td>3.43</td>
</tr>
<tr>
<td>F.D.</td>
<td>97</td>
<td>3.35</td>
<td>83</td>
<td>18/8, 13</td>
<td>127/72, 95</td>
<td>89</td>
<td>4.39</td>
</tr>
<tr>
<td>Average</td>
<td>97</td>
<td>3.45</td>
<td>80</td>
<td>20/9, 14</td>
<td>132/75, 99</td>
<td>80</td>
<td>4.11</td>
</tr>
</tbody>
</table>

at the alveolar-capillary level. To facilitate reequilibration after change in the composition of inspired gas, a period of 15 to 25 minutes was allowed to elapse between the time of introduction of the new inspired mixture and the start of collection of blood and expired gas samples. Two consecutive measurements of blood flow were made in rapid succession after equilibration with each inspired gas mixture. The specific hypoxic mixture administered was selected on the basis of prior performance with hypoxic mixtures. Thus, whereas 6 subjects in table 1 (G.H., H.P., H.M., O.S., W.M., and A.P.) were able to fulfill the criteria for the steady state while breathing a mixture of 12 per cent oxygen in nitrogen, 4 (B.J., E.J., F.D., and C.D.) required a 14 per cent oxygen mixture. The graded exercises were performed with the subject in the supine position, breathing ambient air. The exercise consisted of the alternate flexion and extension of each leg in time with a metronome, thereby moving, with each stroke, an attached leg weight through a fixed distance. Various weights and frequency of leg motion
were used; these were selected, on the basis of prior performance, so as to double or triple the resting oxygen uptake. At least 5 minutes of stable exercise were allowed to elapse before collection of the samples necessary for measurement of pulmonary blood flow. The second level of exercise followed the first without interruption; an increase in work was accomplished by adding weights to each pulley system and by accelerating the frequency of leg strokes. Objective evidence for the accomplishment of the steady state included stabilization of the heart rate and \( V_e \) by the end of the exercise period, and a value for \( R_e \) of approximately 1.0 during the collection period.

Blood and gas samples were drawn anaerobically. The blood samples were analyzed in rapid succession for oxygen content and capacity, and carbon dioxide content by the method of Van Slyke and Neill; the latter data, in conjunction with the arterial blood pH determined by a McInnes-Belcher glass electrode and the line charts of Van Slyke and Sendroy, were used for the calculation of arterial blood \( P_{CO_2} \). The gas samples were analyzed for their oxygen and carbon dioxide content, by means of a micro-Scholander 0.5-ml analyzer. All samples were required to check in duplicate, i.e., within 0.2 volume per cent for expired gases and 0.01 unit for pH.

**Subjects**

The subjects will be considered according to the experiments in which they participated:

1. **Acute Bilateral Hypoxia.** Ten subjects, (tables 1-3), either entirely free of heart and lung disease, or with minimal tuberculous lesions, were included in this group. In these experiments, 2 separate control periods were followed by 2 successive periods of hypoxia.

2. **Graded Exercise.** Three of the 10 subjects (E.J., H.P., and G.H.) and 4 others (tables 4 and 5) underwent 2 consecutive periods of graded exercise following 2 control periods at rest; 1 of these subjects (G.H.) was slightly anemic (table 5).

3. **Graded Exercise Followed by Acute Hypoxia.** In 3 of the subjects (B.J., H.P., and G.H.), the periods of exercise were followed in succession by a period of rest, an additional period of breathing ambient air, and a final period during which a hypoxic mixture was breathed (tables 2 and 5). For the sake of comparison, 3 patients with restricted vascular beds were studied in a similar fashion: 2 (W.E. and L.O.) had undergone pneumonectomy for unilateral suppurative disease; 1 (A.G.) suffered from chronic obstructive pulmonary emphysema (table 6).

4. **Bilateral Stellate Ganglionectomy.** In 1 subject (H.P.) the above sequence of exercise and hypoxia was repeated following bilateral stellate and upper thoracic (T-1 to T-4) ganglionectomy for Raynaud’s syndrome; the operation on the right side also included resection of the middle cervical ganglion and T-5.

**Results**

**Observations on the Effects of Acute Bilateral Hypoxia**

**Ventilation and Gas Exchange**

The changes in minute ventilation \( (V_e) \), oxygen uptake \( (V_{O_2}) \) and respiratory exchange ratio \( (R_e) \) for 10 subjects during low-oxygen breathing are listed in table 1. Each value in this table is the average of 2 consecutive periods. The average increment in \( V_e \) was 22 per cent and in \( V_{O_2} \) was 6 per cent. The average increase in \( R_e \) during the hypoxic periods was .05.

**Arterial Blood Oxyhemoglobin Saturation \( (S_a_{O_2})\)**

In table 2, the patients are listed according to the level of \( S_a_{O_2} \) that obtained during acute hypoxia. As may be seen in this table, the \( S_a_{O_2} \) during the breathing of ambient air averaged 97 per cent; during low-oxygen breathing, the \( S_a_{O_2} \) ranged from 89 to 66 per cent.

**Cardiac Output**

As may also be seen in table 2, the cardiac outputs during breathing of ambient air were within normal limits in all but 2 subjects (O.S. and E.J.) in whom they were slightly elevated; during low-oxygen breathing there was an average increase of 19 per cent; this increase is statistically significant \( (p<.01) \). The relation between the decrease in arterial oxygen saturation and the increase in cardiac output is illustrated in figure 1. In all but 2

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**Table 3**

Relation between the Degree of Systemic Hypoxia and Pulmonary Artery Blood Flow and Pressure in Ten Normal Subjects

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Arterial blood ( \text{O}_2 \text{ sat. during hypoxia} )</th>
<th>Average increase in cardiac output %</th>
<th>Average increase in pulmonary artery pressure \text{mm. Hg}</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>&lt;85</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>&gt;85</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

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Figure 1
The relationship between the change in the oxyhemoglobin saturation of arterial blood and the change in cardiac output in 10 normal subjects. The control values appear as circles; the values during acute hypoxemia are represented by the tips of the arrows. In general, the cardiac output increased during systemic arterial hypoxemia.

Figure 2
The relationship between the change in the oxyhemoglobin saturation of arterial blood and the change in pulmonary arterial mean blood pressure. Symbols as in figure 1. In general, the pulmonary arterial blood pressure increased during systemic arterial hypoxemia.

of the patients (B.J. and E.J.), the increment in cardiac output exceeded 9 per cent, a value previously established in this laboratory as the upper limit of normal variation between consecutive measurements during the breathing of ambient air.¹⁰

Table 4
Changes in Ventilation and Gas Exchange during Graded Exercise in Seven Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr</th>
<th>Sex</th>
<th>BSA, M²</th>
<th>Rest</th>
<th>Exercise 1</th>
<th>Exercise 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L/min/M²</td>
<td>ml/min/M²</td>
<td>L/min/M²</td>
</tr>
<tr>
<td>J.B.</td>
<td>25</td>
<td>M</td>
<td>1.77</td>
<td>3.53</td>
<td>144 .79</td>
<td>6.37</td>
</tr>
<tr>
<td>B.J.</td>
<td>25</td>
<td>M</td>
<td>1.88</td>
<td>4.18</td>
<td>147 .84</td>
<td>7.24</td>
</tr>
<tr>
<td>J.C.</td>
<td>49</td>
<td>M</td>
<td>1.80</td>
<td>4.11</td>
<td>125 .88</td>
<td>9.24</td>
</tr>
<tr>
<td>D.C.</td>
<td>36</td>
<td>F</td>
<td>1.63</td>
<td>2.37</td>
<td>111 .75</td>
<td>3.72</td>
</tr>
<tr>
<td>H.P.</td>
<td>44</td>
<td>F</td>
<td>1.56</td>
<td>4.61</td>
<td>125 .81</td>
<td>7.16</td>
</tr>
<tr>
<td>M.M.</td>
<td>28</td>
<td>M</td>
<td>1.51</td>
<td>3.59</td>
<td>123 .89</td>
<td>9.42</td>
</tr>
<tr>
<td>G.H.</td>
<td>35</td>
<td>F</td>
<td>1.54</td>
<td>4.25</td>
<td>140 .84</td>
<td>5.35</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td>3.80</td>
<td>131 .83</td>
<td>6.93</td>
</tr>
</tbody>
</table>

*Values for \( \dot{V}_O_2 \) are approximate due to high respiratory exchange ratios.

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Table 5
Effects of Graded Exercise on Cardiac Output, Pulmonary and Systemic Artery Blood Pressures in Seven Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Average Cardiac Output (L/min.)</th>
<th>Cardiac Output (L/min.)</th>
<th>Pulmonary Artery Pressure (mm. Hg)</th>
<th>Exercise 1</th>
<th>Exercise 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise 1</td>
<td>Rest</td>
<td>Exercise 1</td>
<td>Rest</td>
</tr>
<tr>
<td></td>
<td>M. M.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are not calculated by Fick equation owing to high Rch; see table 4.

Observations on the Effects of Graded Exercise

There was no consistent pattern of change in systemic blood pressures during hypoxia and average blood pressures for the entire group remained unchanged.

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Cardiac Output

The measurement of the resting cardiac output was inadvertently omitted in 1 subject (D.C.). In the other subjects of table 5, the cardiac outputs were either normal or slightly high at rest. During exercise, the cardiac outputs increased normally, approximately 1 liter increase in flow per 0.1 liter increase in oxygen uptake.

Pulmonary Artery Pressures

As indicated in table 5, pulmonary artery mean pressures were normal at rest and increased, on the average, by 3 mm. Hg during the first exercise period; the increment in mean pressure was associated with a rise in systolic pressure of 3 mm. Hg without change in diastolic pressure. Despite another increment in cardiac output during the second exercise period, there was, on the average, no further increase in pressure. In figure 4 is illustrated the relation between the successive increments in cardiac output and the pulmonary artery pressure. It is clear from a consideration of tables 2 and 5 that, despite larger blood flows, exercise was associated with lower pulmonary artery pressures than was hypoxia.

A distinction also exists not only in the final levels of pulmonary artery pressure, but also in the patterns of change. During hypoxia, there was a gradual rise in pulmonary artery pressure, generally requiring 1 to 3 minutes to achieve the peak, followed by a plateau; this pattern presumably reflects the gradual reduction in the level of alveolar oxygen tension following acute exposure to a low-oxygen mixture. On the other hand, 2 different patterns were noted in the 3 subjects who manifested an appreciable rise in mean pulmonary artery pressure during the first period of exercise; thus 2 (B.J. and H.P.) reached peak pressures within 15 to 30 seconds following the start of exercise, whereas 1 (D.C.) required 2 minutes to achieve peak levels. The changes in pressure were documented by continuous pressure tracings recorded during rest, exercise, rest, and hypoxia. The contrasting pattern between the abrupt increment during exercise and the gradual increment during hypoxia is illustrated for subject H.P. in figure 5; this figure also illustrates the general pattern of pulmonary arterial pressures during the second exercise period.

In the subjects who manifested an abrupt rise in pulmonary artery pressure with the start of exercise, an attempt was made to assess indirectly the role of an increment in pulmonary blood volume in effecting this

---

Table 6

<table>
<thead>
<tr>
<th>Cardiac output</th>
<th>Pulmonary artery mean pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.E. 1 normal lung</td>
<td>Control L/min./M²</td>
</tr>
<tr>
<td>2.77</td>
<td>3.54</td>
</tr>
<tr>
<td>L.O. 1 normal lung</td>
<td>3.01</td>
</tr>
<tr>
<td>A.G. Chronic obstructive emphysema</td>
<td>3.42</td>
</tr>
</tbody>
</table>

*All subjects breathed 12 per cent O₂ in N₂; the arterial blood O₂ saturations were 73, 71, and 81 per cent, respectively.

†During exercise, subjects W.E. and L.O. maintained 96 to 98 per cent O₂ saturation in arterial blood while breathing ambient air; subject A.G. was given 25 per cent O₂ in N₂ as the inspired mixture during exercise to maintain 96 per cent O₂ saturation.
increase: the legs were suddenly but passively raised while the subjects maintained an uninterrupted breathing pattern under pneumo-tachygraphic control. In neither of these subjects did this maneuver elicit a rise in pulmonary artery pressure.

**Brachial Artery Pressures**

As may be seen in table 5, brachial artery pressures were normal at rest, and increased somewhat during the successive periods of graded exercise.

**Observations on the Effects of Acute Bilateral Hypoxia and of Graded Exercise in the Same Subjects**

In order to compare the effects of acute hypoxia and graded exercise in the *same* subjects, 3 normal subjects (B.J., G.H., and H.P.) and 3 patients with restricted vascular beds (W.E., L.O., and A.G.) were subjected to acute hypoxia after 2 consecutive periods of exercise and a second control period. The data for the normal subjects are contained in tables 1, 2, 4, and 5; the pertinent data for the 3 patients are listed in table 6. At equivalent levels of cardiac output, the normal subjects manifested higher pulmonary artery pressures during hypoxia than during exercise (fig. 6); on the other hand, in the patients, equal increments in blood flow, regardless of their induction by either exercise or hypoxia, elicited linear and equivalent increments in pulmonary artery pressure.

In the 3 normal subjects, similar mixed venous blood oxygen tensions obtained during one level of the graded exercise and during acute hypoxia. Although the blood entering the lungs during these 2 experimental situations is similar with respect to oxygen tension, actually the areas of the vascular bed affected by the hypoxic stimulus differ considerably. Thus, as may be seen in figure 7, hypoxia induced by airway affects the entire pulmonary vascular tree, whereas, during exercise, the hypoxia of the mixed venous blood is confined almost exclusively to the pre-capillary bed, since hypoxia is abolished promptly once the blood enters the pulmonary capillary bed. In these subjects, despite the same mixed venous oxygen tensions, the larger blood flows during exercise were associated with lower pulmonary artery mean pressures than during acute hypoxia.

**Observations on the Effects of Bilateral Stellate Ganglionectionomy**

The observations on patient H.P. during exercise and acute hypoxia were repeated 6 weeks following partial cervicodorsal sympa-
thectomy for Raynaud's syndrome. The circulatory responses prior to and following ganglionectomy are illustrated in figure 5. The preoperative measurements, particularly the abrupt rise in pulmonary artery pressure with the onset of exercise, as contrasted with the gradual increase during hypoxia, have already been noted. Similarly, the inordinate increment in pressure during acute hypoxia for the increment in blood flow has also been mentioned. Following sympathectomy, despite somewhat higher original levels of blood flow, the general pattern of response to both acute hypoxia and exercise remained unchanged.

Discussion

The present paper is concerned with the factors that determine pressure-flow relationships in the pulmonary circulation during acute hypoxia and exercise. The results support the view that the contribution of an increase in pulmonary blood flow to this response is small and also provide some evidence that the sympathetic ganglia are not essential for the pressor effect. They leave for other studies\textsuperscript{11-13} to establish if, and how, local hypoxia affects the different pulmonary vascular segments.

Relationship of the Increase in Pulmonary Blood Flow to the Rise in Pulmonary Arterial Blood Pressure during Acute Hypoxia

It is now well known that the pressure-flow relationship of the normal pulmonary arterial tree is such that an appreciable increase in pulmonary blood flow is accommodated with only a barely perceptible increment in pulmonary arterial blood pressure.\textsuperscript{14-22} In the present study, blood flow was measured by the Fick principle in such a way as to avoid the multiplicity of potential errors.\textsuperscript{25-27} By comparing the effects of graded exercise and acute hypoxia, particularly in the same subjects, it was possible to show that the increment in pulmonary blood flow during acute hypoxia is insufficient to account for the rise in pulmonary arterial blood pressure in normal subjects. By way of contrast, severe curtailment of the pulmonary vascular bed may so alter the pressure-flow characteristics of the lung that a slight increment in blood flow...
flow will elicit inordinate increments in pulmonary arterial blood pressure. It is of interest in this regard, that only under conditions of severe restriction of the pulmonary vascular bed may a linear relationship between blood pressure and flow exist. Moreover, under this circumstance, it would be expected that the pressor effect of mild vasomotor activity would be obscured by the mechanical effects of an increase in blood flow in a restricted vascular bed. Such observations emphasize that the pressure-flow curve must be established for each subject separately in order to interpret changes in pulmonary vascular resistance to blood flow.

The patterns of change in pulmonary blood flow during exercise are similar to those that have recently been described by others.19-21 The present studies are in accord with these observations, both with respect to the time-sequence of changes and the relationship between oxygen uptake and cardiac output.

Furthermore, through the use of continuous records of pulmonary arterial blood pressure during exercise, the present studies support the view that the pulmonary arterial blood pressure rises slightly, but consistently, during exercise.18, 19, 21 Of particular interest is the failure of the second level of exercise, with pulmonary blood flows of twice normal, to evoke a further rise in pulmonary arterial pressure in the normal subjects. The plateau in pressure may be related to widening of patent pulmonary vessels by the increased ventilatory efforts of exercise, to accelerated flow through the center of vessels of unchanged size or to opening of new vessels. These observations do not distinguish between these prospects.

Role of the Autonomic Nervous System in Mediating the Pulmonary Arterial Pressure Response to Acute Hypoxia

Others have implicated the sympathetic innervation of the lung, operating under the
influence of the systemic chemoceptors, in the genesis of the pulmonary hypertension of acute hypoxia.\textsuperscript{28} In the present study of a subject with extensive sympathectomy for Raynaud's phenomena, the pattern of the pulmonary pressor response to acute hypoxia was indistinguishable from the normal. This type of response has since been duplicated in another patient with even more extensive sympathectomy.\textsuperscript{29} These observations, particularly when coupled with others concerning the persistence of the pressor response following the administration of atropine\textsuperscript{11,12} provide no support for the hypothesis that the autonomic nervous system is involved in the pulmonary hypertension of human subjects who are exposed to acute hypoxia.

Other Mechanisms Involved in the Pressor Response to Acute Hypoxia

It is clear that the present study has sufficed mainly to exclude certain mechanical and nervous factors as prime movers in the pulmonary hypertensive response to acute hypoxia. In the accompanying paper, the role of the pulmonary blood volume is considered. The present study also suggests that the pulmonary pressor response to acute hypoxia involves a change in the distensibility and in the dimensions of some segment of the pulmonary vascular tree. Other studies, particularly those concerned with the relief, by acetycholine, of the pulmonary hypertension of acute hypoxia\textsuperscript{24, 30, 31} as well as that of chronic lung and heart disease\textsuperscript{32} suggest that vasomotor activity may be involved in the pulmonary pressor response to acute hypoxia. However, the exact site and mode of action of the hypoxic stimulus remain to be uncovered.\textsuperscript{33, 34}

Summary

The effects of acute hypoxia, of graded exercise, or both, on the pulmonary circulation were studied in 17 normal subjects. In 3 of these subjects, and in 3 patients with restricted vascular beds, the effects of these stimuli were compared during successive test periods.

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related to the increase in pulmonary blood flow.

In 1 subject, the surgical resection of the preganglionic fibers and ganglia which supply sympathetic effere\textsuperscript{t}e nerves to the pulmonary vascular tree was without effect on the responses of the pulmonary circulation to acute hypoxia and to exercise.

The present study failed to identify the mechanism and the site of action of acute hypoxia on the pulmonary circulation.

**Summario in Interlingua**

Le effects de acute hypoxia, de graduate exercitio, e de un combination del duo super le circulation pulmonar esseva studiati in 17 subjectos normal. In 3 de iste subjectos e in 3 patientes con restringite vasculatura le effects del mentionate stimulos esseva comparete durante successive periodos de testatia.

In 7 normales, moderate formas de exercitio—associate con un augmento del rendimento cardiac de approximativemente 25 pro cento—resultava in un augmento medie del tension pulmono-arterial medie de 3 mm de Hg. Plus intense formas de exercitio in le mesme subjectos—associate con un augmento additional del rendimento cardiac de de novo approximativamente 25 pro cento—non evocava un augmento additional in le tension pulmono-arterial medie.

Per contrasto con isto, 10 subjectos con normalitate del circulation pulmonar—qui respondeva a acute hypoxia per un reduction medie del saturation oxygenie in le sanguine arterial de 17 pro cento—manifestava un augmento medie del tension cardiac de 5 pro cento e un augmento medie del tension pulmono-arterial medie de 4 mm de Hg. Le nivello critica de saturation oxygenie in le sanguine arterial pro un augmento significative del tension pulmono-arterial esseva 85 pro cento. In 6 subjectos in qui le saturation oxygenie in le sanguine arterial esseva reducita a infra le nivello critica de 85 pro cento, le augmento medie del tension pulmono-arterial medie amontava a 7 mm de Hg.

In le 3 subjectos qui haberava normal circulationes pulmonar e qui esseva subjicite a exercitio hypoxia, le effects contrari de iste duo stimulos in le circulation pulmonar esseva frappant. In le 3 patientes con restringite vasculaturas, le exposition successive a ille duo stimulos produciva un augmento del tension pulmono-arterial medie que pareva esser relationate linearmente al augmento del fluxo de sanguine pulmonar.

In 1 subjecto, le resection chirurgie del fibras preganglionic e del gangliones que provide efferente nervos sympathique al vasculatura pulmonar remaneva sin effecto super le responsas del circulation pulmonar a acute hypoxia e a exercitio.

Le presente studio non resultava in un identification del mechanismo e del sito de action del effecto de acute hypoxia super le circulation pulmonar.

**References**


HYPOXIA AND PULMONARY CIRCULATION


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