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 dog2 and by von Euler and Liljestrand in the cat,2-4 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,2-4 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 animals6 and in man,6 attempts to reproduce the pulmonary pressor response to acute hypercapnia have yielded far less consistent results.7

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 manner8 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 (\(V_o_2\)), the respiratory exchange ratio (\(R_e\)), 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.”9 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 \(R_e\), \(V_o_2\)) for the equality of gas exchange measured at the mouth to that occurring.
HYPOXIA AND PULMONARY CIRCULATION

Table 1
Changes in Ventilation and Gas Exchange during Acute Hypoxia in Ten Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Breathing mixture: Ambient air</th>
<th>Breathing mixture: 12-14% O₂ in N₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>O.S.</td>
<td>35</td>
<td>M</td>
<td>1.77, 4.27, 138, .85, 5.26, 147, .90</td>
<td></td>
</tr>
<tr>
<td>A.P.</td>
<td>48</td>
<td>M</td>
<td>1.78, 5.08, 129, .91, 6.25, 132, .98</td>
<td></td>
</tr>
<tr>
<td>W.M.</td>
<td>49</td>
<td>M</td>
<td>1.76, 5.73, 136, .92, 7.04, 147, .94</td>
<td></td>
</tr>
<tr>
<td>H.P.</td>
<td>44</td>
<td>F</td>
<td>1.56, 4.61, 125, .81, 5.64, 129, .90</td>
<td></td>
</tr>
<tr>
<td>H.M.</td>
<td>35</td>
<td>M</td>
<td>2.10, 3.38, 118, .88, 4.12, 127, .98</td>
<td></td>
</tr>
<tr>
<td>G.H.</td>
<td>35</td>
<td>F</td>
<td>1.54, 4.25, 140, .84, 5.96, 147, .94</td>
<td></td>
</tr>
<tr>
<td>E.J.</td>
<td>68</td>
<td>M</td>
<td>1.58, 4.51, 131, .86, 5.03, 132, .91</td>
<td></td>
</tr>
<tr>
<td>C.D.</td>
<td>51</td>
<td>M</td>
<td>1.71, 4.20, 140, .84, 5.96, 147, .94</td>
<td></td>
</tr>
<tr>
<td>B.J.</td>
<td>25</td>
<td>M</td>
<td>1.88, 4.18, 147, .84, 4.61, 148, .93</td>
<td></td>
</tr>
<tr>
<td>F.D.</td>
<td>48</td>
<td>M</td>
<td>1.80, 4.96, 124, .94, 6.51, 149, 1.04</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td>4.52, 129, .87, 5.51, 137, .92</td>
<td></td>
</tr>
</tbody>
</table>

V_{E}, minute ventilation; \( \dot{V}_{O_2} \), oxygen uptake; Re, 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 O₂ sat., %</th>
<th>Cardiac output, L/min./M²</th>
<th>Heart rate, per min.</th>
<th>Pulmonary arterial pressure, mm. Hg</th>
<th>Arterial blood O₂ sat., %</th>
<th>Cardiac output, L/min./M²</th>
<th>Heart rate, per min.</th>
<th>Pulmonary arterial pressure, mm. Hg</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>66</td>
<td>5.26</td>
<td>96</td>
<td>33/17, 24</td>
</tr>
<tr>
<td>A.P.</td>
<td>95</td>
<td>3.26</td>
<td>83</td>
<td>12/6, 9</td>
<td>70</td>
<td>3.08</td>
<td>83</td>
<td>19/11, 15</td>
</tr>
<tr>
<td>W.M.</td>
<td>96</td>
<td>3.41</td>
<td>83</td>
<td>28/11, 18</td>
<td>74</td>
<td>4.87</td>
<td>93</td>
<td>30/12, 20</td>
</tr>
<tr>
<td>H.P.</td>
<td>95</td>
<td>2.86</td>
<td>80</td>
<td>22/11, 16</td>
<td>76</td>
<td>3.22</td>
<td>88</td>
<td>27/12, 20</td>
</tr>
<tr>
<td>H.M.</td>
<td>98</td>
<td>2.63</td>
<td>67</td>
<td>27/11, 18</td>
<td>78</td>
<td>3.43</td>
<td>78</td>
<td>48/18, 31</td>
</tr>
<tr>
<td>G.H.</td>
<td>98</td>
<td>3.88</td>
<td>82</td>
<td>13/7, 10</td>
<td>84</td>
<td>4.08</td>
<td>96</td>
<td>18/9, 15</td>
</tr>
<tr>
<td>E.J.</td>
<td>95</td>
<td>4.30</td>
<td>80</td>
<td>16/6, 11</td>
<td>85</td>
<td>4.68</td>
<td>92</td>
<td>21/9, 14</td>
</tr>
<tr>
<td>C.D.</td>
<td>95</td>
<td>2.78</td>
<td>73</td>
<td>18/9, 13</td>
<td>86</td>
<td>4.01</td>
<td>75</td>
<td>18/9, 13</td>
</tr>
<tr>
<td>B.J.</td>
<td>98</td>
<td>3.43</td>
<td>78</td>
<td>20/10, 14</td>
<td>87</td>
<td>3.43</td>
<td>79</td>
<td>23/11, 17</td>
</tr>
<tr>
<td>F.D.</td>
<td>97</td>
<td>3.35</td>
<td>83</td>
<td>18/8, 13</td>
<td>89</td>
<td>4.39</td>
<td>88</td>
<td>17/7, 12</td>
</tr>
<tr>
<td>Average</td>
<td>97</td>
<td>3.45</td>
<td>80</td>
<td>20/9, 14</td>
<td>80</td>
<td>4.11</td>
<td>87</td>
<td>25/12, 18</td>
</tr>
</tbody>
</table>

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

---

**Table 3**

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Arterial blood ( O_2 ) sat. during hypoxia %</th>
<th>Average increase in cardiac output %</th>
<th>Average increase in pulmonary artery pressure 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>
HYPOXIA AND PULMONARY CIRCULATION

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.

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, y.m.</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></td>
<td>L/min/M²</td>
<td>ml/min/M²</td>
</tr>
<tr>
<td>J.B.</td>
<td>25</td>
<td>M</td>
<td>1.77</td>
<td></td>
<td>3.53</td>
<td>144</td>
</tr>
<tr>
<td>B.J.</td>
<td>25</td>
<td>M</td>
<td>1.88</td>
<td></td>
<td>4.18</td>
<td>147</td>
</tr>
<tr>
<td>J.C.</td>
<td>49</td>
<td>M</td>
<td>1.80</td>
<td></td>
<td>4.11</td>
<td>125</td>
</tr>
<tr>
<td>D.C.</td>
<td>36</td>
<td>F</td>
<td>1.63</td>
<td></td>
<td>2.37</td>
<td>111</td>
</tr>
<tr>
<td>H.P.</td>
<td>44</td>
<td>F</td>
<td>1.56</td>
<td></td>
<td>4.61</td>
<td>125</td>
</tr>
<tr>
<td>M.M.</td>
<td>28</td>
<td>M</td>
<td>1.51</td>
<td></td>
<td>3.59</td>
<td>123</td>
</tr>
<tr>
<td>G.H.</td>
<td>35</td>
<td>F</td>
<td>1.54</td>
<td></td>
<td>4.25</td>
<td>140</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.80</td>
<td>131</td>
</tr>
</tbody>
</table>

*Values for V̇O₂ 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>Arterial Blood Oxygenation Saturation</th>
<th>Cardiac output, L. min.</th>
<th>Heart rate</th>
<th>Pulmonary arterial pressure, mm Hg</th>
<th>Pulmonary venous pressure, mm Hg</th>
<th>Systemic arterial pressure, mm Hg</th>
<th>Systemic venous pressure, mm Hg</th>
<th>Coronary arterial pressure, mm Hg</th>
<th>Coronary venous pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.B.</td>
<td>20.2</td>
<td>4.14</td>
<td>74</td>
<td>23/9, 16</td>
<td>113/61, 83</td>
<td>125/68, 86</td>
<td>139/73, 95</td>
<td>132/69, 91</td>
<td>132/69, 91</td>
</tr>
<tr>
<td>B.J.</td>
<td>19.5</td>
<td>3.43</td>
<td>78</td>
<td>20/10, 14</td>
<td>143/80, 100</td>
<td>139/73, 95</td>
<td>132/69, 91</td>
<td>140/72, 99</td>
<td>112/74, 95</td>
</tr>
<tr>
<td>J.C.</td>
<td>18.5</td>
<td>2.85</td>
<td>73</td>
<td>20/9, 14</td>
<td>104/71, 88</td>
<td>123/68, 98</td>
<td>132/75, 105</td>
<td>128/83, 105</td>
<td>128/83, 105</td>
</tr>
<tr>
<td>Average</td>
<td>(3.41)</td>
<td>(79)</td>
<td>(121/74, 95)</td>
<td>(21/10, 16)</td>
<td>(125/76, 99)</td>
<td>(125/76, 99)</td>
<td>(125/76, 99)</td>
<td>(125/76, 99)</td>
<td>(125/76, 99)</td>
</tr>
</tbody>
</table>

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

In all of these subjects, the arterial blood oxygenation saturation was normal at rest (95 to 99 per cent) and remained either unaltered or increased during exercise.

In all of these subjects, the arterial blood oxygenation saturation was normal at rest (95 to 99 per cent) and remained either unaltered or increased during exercise.
Table 6

Pulmonary Artery Blood Flows and Pressures during Acute Hypoxia and Exercise in Three Patients with Restricted Vascular Beds Studied during the "Steady State"

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Cardiac output</th>
<th>Pulmonary artery mean pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control L/min. M²</td>
<td>Hypoxia* L/min. M²</td>
</tr>
<tr>
<td>W.E.</td>
<td>1 normal lung</td>
<td>2.77</td>
<td>3.54</td>
</tr>
<tr>
<td>L.O.</td>
<td>1 normal lung</td>
<td>3.01</td>
<td>3.48</td>
</tr>
<tr>
<td>A.G.</td>
<td>Chronic obstructive emphysema</td>
<td>3.42</td>
<td>3.75</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.

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
increase: the legs were suddenly but passively raised while the subjects maintained an uninterrupted breathing pattern under pneumotachygraphic 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 precapillary 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 Ganglionectomy**

The observations on patient H.P. during exercise and acute hypoxia were repeated 6 weeks following partial cervicodorsal sympa-
hypoxia 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 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. In the present study, blood flow was measured by the Fick principle in such a way as to avoid the multiplicity of potential errors. 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 could be the cause of a large increase in pulmonary arterial blood pressure.
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 chemoreceptors, in the
genesis of the pulmonary hypertension of
acute hypoxia.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.29 These observations, particu-
larly when coupled with others concerning
the persistence of the pressor response fol-
lowing the administration of atropine,11,12 pro-
vide 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 pul-
monary hypertensive response to acute hy-
oxia. In the accompanying paper, the role of
the pulmonary blood volume is considered.
The present study also suggests that the pul-
monary 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, par-
cularly those concerned with the relief, by
acetylcholine, of the pulmonary hypertension
of acute hypoxia24, 30, 31 as well as that of
chronic lung and heart disease32 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 un-
covered.33, 34

Summary

The effects of acute hypoxia, of graded
exercise, or both, on the pulmonary circu-
lation 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.

* Circulation, Volume XXII, August 1960

<table>
<thead>
<tr>
<th></th>
<th>Exercise</th>
<th>12% Oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean PA Pressure (mm Hg)</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Mean Cardiac Index (liters/min/m²)</td>
<td>4.67</td>
<td>3.54</td>
</tr>
</tbody>
</table>

Figure 7

Mean pulmonary arterial pressure and flow in 4 normal subjects at same mixed venous PO₂ during exercise and hypoxia. Schematic representation of the difference between the pulmonary vascular seg-
ments which are rendered hypoxic by exercise and by low-oxygen breathing.

In 7 normal subjects, moderate exercise,
associated with an increase in cardiac output
of approximately 25 per cent, resulted in an
average rise in pulmonary arterial mean pres-
sure of 3 mm Hg. More strenuous exercise in
the same subjects, associated with a further
increase in cardiac output of approximately
25 per cent, did not elicit further increment
in pulmonary arterial mean pressure.

In contrast, 10 subjects with normal pul-
monary circulations, who responded to acute
hypoxia with an average reduction of arterial
oxygen saturation of 17 per cent, manifested
an average increase in cardiac output of 5
per cent and an average rise in mean pul-
monary arterial pressure of 4 mm Hg. The
critical level of arterial blood oxygen satu-
ration for a significant rise in pulmonary arte-
rial pressure was 85 per cent: in 6 subjects,
with arterial blood O₂ saturation reduced be-
low this level, the average pulmonary artery
pressure rise was 7 mm Hg.

In the 3 subjects with normal pulmonary
circulations who performed exercise and were
exposed to acute hypoxia, the contrasting ef-
fects of these stimuli on the pulmonary circu-
lation were striking. In the 3 patients with
restricted vascular beds exposed successively
to both stimuli, the rise in pulmonary arte-
rial mean pressure appeared to be linearly
related to the increase in pulmonary blood flow.

In 1 subject, the surgical resection of the preganglionic fibers and ganglia which supply sympathetic efferent 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 effetti de acute hypoxia, de graduate exercitio, e de un combination del duo super le circulación pulmonar esseva studiade in 17 subjectos normal. In 3 de iste subjectos e in 3 patientes con restringite vasculatura le effetti del mencionate stimuloses esseva comparate durante successive periodos de testation.

In 7 normales, moderate formas de exercitio—associate con un augmento del rendimento cardiae de approximativamentemente 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 same subjectos—associate con un augmento addicional del rendimento cardiae de de novo approximativamente 25 pro cento—non evocava ulle augmento addicional in le tension pulmono-arterial medie.

Per contrasto con ista, 10 subjectos con normalitate del circulación 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 rendimento cardiae de 5 pro cento e un augmento medie del tension pulmono-arterial medie de 4 mm de Hg. Le nivello critic de saturation oxygenie in le sanguine arterial pro un augmento significativa del tension pulmono-arterial esseva 85 pro cento. In 6 subjectos in qui le saturation oxygenie in le sanguine arterial esseva reducute a infra le nivello critic de 85 pro cento, le augmento medie del tension pulmono-arterial medie amontava a 7 mm de Hg.

In le 3 subjectos qui habeva normal circulationes pulmonar e qui esseva subjicite a exercitio e hypoxia, le effetti contrari de iste duo stimulosi in le circulación pulmonar esseva frappante. In le 3 patientes con restringite vasculaturas, le exposition successive a ille duo stimulosi produceva un augmento del tension pulmono-arterial medie que pareva esser relationate lineamente al augmento del fluxo de sanguine pulmonar.

In 1 subjecto, le resection chirurgie del fibras pre-ganglionie e del gangliones que provide efferente nervos sympathic al vasculatura pulmonar remaneva sin effecto super le responsas del circulación pulmonar a acute hypoxia e a exercitio.

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

**References**


Effects of Acute Hypoxia and Exercise on the Pulmonary Circulation
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