The Pulmonary Vascular Responses to Short-Term Hypoxia in Human Subjects

By Joseph T. Doyle, M.D., Joseph S. Wilson, M.D., and James V. Warren, M.D.

Using the catheter technic, the acute circulatory reactions to a brief period of hypoxia have been studied. It was found that when a normal person breathed a gas mixture containing only 10 per cent oxygen, the pulmonary arterial pressure rose but the pulmonary capillary pressure remained unchanged. This indicated pulmonary vasoconstriction, thought to be due to a direct effect on the pulmonary vascular tree. No demonstrable change in so-called pulmonary blood volume could be detected. In an additional group of patients with cardiopulmonary disease the reactions were more erratic but not significantly different in type.

In certain patients with heart disease pulmonary hypertension occurs in association with a remarkably steep pulmonary arteriocapillary pressure gradient suggestive of a vasoconstrictive mechanism. It has been demonstrated in normal human subjects that acute hypoxia induces a considerable pulmonary hypertension; but the mechanism of this has not been elucidated. It was thought desirable to make further observations on the mechanism of hypoxic pulmonary hypertension in normal subjects and in patients with cardiopulmonary disease with particular reference to the pressure gradient between the pulmonary artery and the pulmonary capillary bed and to possible changes in the pulmonary blood volume.

Methods

Eight normal adults ranging in age from 27 to 45 years, and 12 individuals with sundry cardiopulmonary abnormalities have been studied. The subjects were either fasting or had had a light breakfast. Mild barbiturate sedation was occasionally employed to allay anxiety or to relieve respiratory distress. The recumbent position was used unless orthopnea required elevation of the shoulders.

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A double lumen catheter was passed into the pulmonary artery by the usual technic. The tip was wedged in an end vessel so that the pulmonary capillary pressure was measured, while the proximal lumen opened into the main pulmonary artery. Simultaneous pressure measurements were made on Sanborn electromanometers and, together with an electrocardiogram and a pneumogram, were inscribed on a Sanborn Poly-viso recorder. A zero point 5 cm. below the sternal angle was arbitrarily selected for pressure measurement. A Cournand needle was inserted into a brachial artery. Blood gas analyses were done by the method of Van Slyke and Neill. The oxygen consumption was determined by the open circuit method of Haldane. The cardiac output was calculated by the Fick principle and also by the dye dilution method of Stewart and Hamilton as modified by Ebert. A carefully measured amount of T-1824 dye was rapidly injected into the proximal lumen of the cardiac catheter and arterial blood was collected for two second periods during the primary circulation. In subjects with a prolonged circulation time the collecting period was suitably lengthened. The optical density of the dyed blood samples was read on a Beckman spectrophotometer. A time-concentration curve was then constructed from which were derived the mean circulation time of the dye, the cardiac output and the so-called pulmonary blood volume. A satisfactory correlation between the results of the direct Fick and of the dye dilution methods has been shown in this and other laboratories. We feel that the dye method is particularly useful and reliable in demonstrating directional changes in cardiac output. The general blood volume was estimated from a 10 minute dye sample, or in the case of subjects with a delayed mixing time, from multiple dye samples.

A BLB* oronasal mask was then applied to the face and 10 per cent oxygen in nitrogen was administered. Continuous or semicontinuous records

* Boothby-Lovelace-Bulbulian.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Surface Area (sq. M.)</th>
<th>Remarks</th>
<th>Hematocrit Reading</th>
<th>Pulse Rate</th>
<th>Pulmonary Arterial Pressure</th>
<th>Pulmonary Arterial Pressure Gradient</th>
<th>Pulmonary Capillary Pressure</th>
<th>Systemic Blood Pressure</th>
<th>Systemic Blood Pressure Saturation</th>
<th>Mean Circulation Time</th>
<th>Arterial Oxygen Consumption</th>
<th>Oxygen Consumption Difference</th>
<th>Cardiac Index</th>
<th>Stroke Volume</th>
<th>Cardiac Output</th>
<th>Pulmonary Blood Flow</th>
<th>Pulmonary Resistance</th>
<th>Right Ventricular Work</th>
<th>Total Peripheral Resistance</th>
<th>Left Ventricular Work</th>
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<td>1.63</td>
<td>Control</td>
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<td>20</td>
<td>10.0</td>
<td>2.5</td>
<td>7.5</td>
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<td>15.8</td>
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<td>2.8</td>
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<td>85</td>
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<td>10.8</td>
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<td>160</td>
<td>95</td>
<td>115</td>
<td>94</td>
<td>9.1</td>
<td>164</td>
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<td>3.8</td>
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<td>92</td>
<td>2810</td>
<td>580</td>
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<td>39</td>
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<td>70</td>
<td>17</td>
<td>7.0</td>
<td>6.0</td>
<td>11.0</td>
<td>130</td>
<td>85</td>
<td>108</td>
<td>93</td>
<td>13.0</td>
<td>102</td>
<td>4.1</td>
<td>2.4</td>
<td>3.3</td>
<td>96</td>
<td>2350</td>
<td>720</td>
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<tr>
<td>Avg.</td>
<td>36</td>
<td>1.82</td>
<td>Control</td>
<td>41.6</td>
<td>81</td>
<td>16</td>
<td>10.0</td>
<td>5.5</td>
<td>5.0</td>
<td>128</td>
<td>79</td>
<td>98</td>
<td>95</td>
<td>11.9</td>
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<td>4.0</td>
<td>3.5</td>
<td>3.4</td>
<td>77</td>
<td>2810</td>
<td>660</td>
</tr>
</tbody>
</table>

**Per cent change**

- +9%  
- +44%  
- +50%  
- ±50%  
- +100%  
- -5%  
- -22%  
- -18%  
- +29%  
- +18%  
- +2%  
- +8%  
- +107%  
- -21%  
- +20%  

**p value**

- .2 < p < .3  
- p < .001  
- p < .001  
- .3 < p < .001  
- .05 < p < .1  
- < .1  
- < .1  
- < .1  
- < .1  
- < .1  
- < .1  
- < .2  
- < .4  
- < .4  
- < .4  
- < .4  
- < .4
were kept of the respiration, heart rate, pulmonary arterial and pulmonary capillary pressures. At about 10 minutes the systemic blood pressure was measured and arterial blood was obtained for determination of oxygen saturation. The cardiac output and the pulmonary blood volume were then re-measured by the dye dilution technic.

Circulatory effects due to the mask itself or to a significant accumulation of carbon dioxide in the dead space were excluded by appropriate procedures.

The vascular resistance of the pulmonary and of the systemic circuits and the work of the ventricles were calculated by the formulas suggested by Dexter. 9

RESULTS

In the normal group (table 1) the inhalation of the low oxygen mixture was followed by a deepening of respiration without much increase in rate, a response characteristic of hypocapnic anoxia. No subject became significantly dyspneic. Cyanosis was only minimal. Wide respiratory variations were imposed on the pressure contours. Within a minute or so there was a rise in the pulmonary arterial mean pressure in which both the systolic and the diastolic pressures participated (fig. 1). On the other hand, the pulmonary capillary pressure was unchanged or fell slightly during the hypoxic period. The gradient of pressure between the pulmonary artery and the pulmonary capillary bed widened slowly and steadily during hypoxia (fig. 1). The systemic arterial pressure was unchanged or fell slightly. The average heart rate rose, although in several individuals there was no change. The circulatory velocity from pulmonary to peripheral artery increased. The cardiac output tended to increase, roughly in proportion to the degree of arterial oxygen unsaturation. The pulmonary blood volume, that is the volume of blood between the main pulmonary artery and all peripheral points temporally equidistant from the point of arterial sampling, was not significantly altered. There was a highly significant increase in the pulmonary vascular resistance, a less significant fall in the systemic vascular resistance, and some increase in the work of the heart.

In the abnormal group (table 2), the circulatory responses to hypoxia were so variable as to render a statistical comparison with the normal group of little value. Almost all of these individuals developed considerable air hunger and several became strikingly cyanotic. Those subjects (cases 1, 3, 8, 9) with an already elevated pulmonary arterial pressure and a correspondingly high pulmonary vascular resistance all showed a further increase in the pulmonary arterial pressure during hypoxia, while the pulmonary capillary pressure remained constant. Since there was an insigniciant increase in the cardiac output in the first three cases, there was a consequent further increase in the pulmonary vascular resistance. In case 9 there was no net increase in the pulmonary vascular resistance since there was a considerable increase in the cardiac output. Frank congestive heart failure was present in subjects 11 and 12. Although the pulmonary pressure gradient increased during hypoxia in these two subjects, there was a substantial increase in the pulmonary capillary pressure associated with a rise in the systemic arterial pressure, suggestive of an aggravation of left ventricular failure. In patient 10, who had isolated mitral stenosis, there was a tremendous rise in the pulmonary vascular resistance and a considerable decrease in the pulmonary capillary pressure during hypoxia, due perhaps to a transient sharp reduction in the volume of blood in the lungs. The other four subjects (cases 2, 4, 5, 6) showed no change in the
### Table 2—Circulatory Responses to Hypoxia of Twelve Individuals with Cardiopulmonary Abnormalities

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Surface Area</th>
<th>Remarks</th>
<th>Pulmonary Arterial Pressure</th>
<th>Systemic Blood Pressure</th>
<th>Cardiac Index</th>
<th>Total Perilobar Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Chronic lung dis.</td>
<td>28</td>
<td>1.29</td>
<td>Control</td>
<td>45.9</td>
<td>120</td>
<td>25</td>
<td>12</td>
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<tr>
<td>2 Lung abscess</td>
<td>50</td>
<td>1.70</td>
<td>Hypoxia 12 min.</td>
<td>28.7</td>
<td>115</td>
<td>26</td>
<td>9</td>
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<tr>
<td>3 Thyroidoxieosis</td>
<td>64</td>
<td>1.57</td>
<td>Control</td>
<td>39.2</td>
<td>94</td>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>4 Smoke inhalation</td>
<td>31</td>
<td>1.78</td>
<td>Hypoxia 14 min.</td>
<td>43.7</td>
<td>90</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>5 Es. hypertension</td>
<td>40</td>
<td>1.55</td>
<td>Control</td>
<td>39.4</td>
<td>95</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>6 Diabetes; anemia</td>
<td>38</td>
<td>1.67</td>
<td>Hypoxia 11 min.</td>
<td>31.3</td>
<td>90</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>7 Ependymitis</td>
<td>24</td>
<td>1.94</td>
<td>Hypoxia 9 min.</td>
<td>45.5</td>
<td>105</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>8 Chronic lung dis.</td>
<td>63</td>
<td>1.41</td>
<td>Hypoxia 13 min.</td>
<td>47.7</td>
<td>95</td>
<td>85</td>
<td>32</td>
</tr>
<tr>
<td>9 Chronic lung dis.</td>
<td>50</td>
<td>1.58</td>
<td>Hypoxia 11 min.</td>
<td>32.7</td>
<td>90</td>
<td>42</td>
<td>14</td>
</tr>
<tr>
<td>10 Mitral stenosis</td>
<td>23</td>
<td>1.48</td>
<td>Hypoxia 8 min.</td>
<td>39.0</td>
<td>98</td>
<td>95</td>
<td>33</td>
</tr>
<tr>
<td>11 Mitral stenosis; CHF</td>
<td>51</td>
<td>1.84</td>
<td>Hypoxia 10 min.</td>
<td>44.4</td>
<td>98</td>
<td>95</td>
<td>33</td>
</tr>
<tr>
<td>12 Acute nephritis</td>
<td>45</td>
<td>1.98</td>
<td>Hypoxia 11 min.</td>
<td>30.3</td>
<td>80</td>
<td>43</td>
<td>14</td>
</tr>
</tbody>
</table>
pulmonary vascular resistance and in only one (case 6) was there a significant increase in the cardiac output. The changes in the pulmonary blood volume in this group appear to have been random. The tendency for the "pulmonary blood volume" to be larger than in the normal group may have been associated with a large left ventricle.

**DISCUSSION**

The production of pulmonary hypertension in our normal subjects by short periods of hypoxia agrees with previously reported studies in animals and in man. Infar as we are aware it has not hitherto been reported that hypoxia does not affect the pulmonary capillary pressure in man. It is of interest that Liljestrand has found that the left atrial pressure in the cat is unaltered by hypoxia. It is now generally agreed that both in animals and in man the pulmonary capillary, the pulmonary venous, the left atrial and the left ventricular end diastolic pressures are of approximately the same magnitude.

The pulmonary pressor response to hypoxia is of rapid onset, as is shown by our studies and by the observations of Motley and of Liljestrand. In this respect the observations of Dirken and Heemstra are difficult to interpret. These workers found only a very gradual reduction in blood flow through the unilaterally hypoxic rabbit lung, but no data are given concerning changes in the vascular pressures or the vascular resistance in that organ.

The cardiac output in the normal individual is shown in our study to be increased by hypoxia. This is in agreement with observations in animals and in man. The slight reduction in the cardiac output in normal man during hypoxia reported by Motley was due to an apparently reduced oxygen consumption. At an altitude of 20,000 feet a period of 50 to 60 minutes is required for the alveolar respiratory quotient to return to the control value. An approximately equivalent time would presumably be required during the inhalation of 10 per cent oxygen. Subsequent observations in Cournand's laboratory have shown that the cardiac output normally increases during hypoxia. The dye dilution technic for determining the cardiac output obviates the problem of achieving a steady state. A fair correlation exists between the intensity of the hypoxia and the increase in the cardiac output in the normal group. Since the systemic blood pressure either is unchanged or declines slightly, the increase in the cardiac output is presumably initiated by the fall in the total peripheral vascular resistance. This increase in the blood flow is the primary compensatory mechanism whereby oxygen transport to the tissues is maintained during hypoxia.

The mechanism of the pulmonary hypertension and of the increase in the pulmonary vascular resistance during hypoxia is not entirely clear. Under our experimental conditions it cannot be explained by the moderate increase in the cardiac output. The absence of a rise in the pulmonary capillary pressure excludes a "back-pressure" effect from the left heart. It has recently been suggested that an increased flow through the bronchial arteries may account for the pulmonary hypertension of hypoxia. Such an occurrence during an acute experiment seems also to be excluded by the failure of the pulmonary capillary pressure to rise during hypoxia, and by the collateral evidence that in the dog the bronchial arterial flow represents less than 1 per cent of the cardiac output. It appears unlikely that the lymphatic drainage from the lungs is significantly impeded by a short period of hypoxia. As pointed out by Motley, respiratory alkalosis cannot account for the pulmonary pressor response; furthermore, where measured in our cases, the changes in arterial and venous carbon dioxide tension and hydrogen ion concentration were not large. The remaining possibility, then, is that acute hypoxia causes a constriction of the pulmonary precapillary vessels. It has been concluded by Liljestrand and by Dirken and Heemstra that the most likely mechanism of this vasoconstriction is a direct effect of the low oxygen tension of the returning venous blood on the walls of the pulmonary arterioles. Figure 2 illustrates rapidly consecutive oximetric observations during induced hypoxia on the systemic arterial and on the right ventricular blood with a simultaneous
continuous pressure recording from the pulmonary artery. There is some suggestion that the pressure changes coincide with the changes in oxygen tension of the venous blood more closely than with those of the arterial blood. The point is difficult to prove. While the results of Dirken and Heemstra12, 13, 21 do not correspond with observations in man, under their experimental conditions they cannot attribute hypoxic pulmonary hypertension to autonomic nervous activity, to changes in carbon dioxide tension, to epinephrine, ergotamine, acetylcholine and physostigmine or histamine.

This diffuse pulmonary vasoconstriction produced in normal individuals by experimental hypoxia is of no obvious value. In lung disease, on the other hand, as pointed out by Liljestrand,11 segmental pulmonary arteriolar constriction in response to a local reduction in oxygen tension should be a useful protective mechanism. By this means arterial oxygen saturation could be maintained by the deflection of the pulmonary arterial stream away from poorly aerated toward better aerated lung tissue.

The circulatory responses to hypoxia of the abnormal subjects follow no pattern. In general, those with a pre-existent pulmonary hypertension showed a further rise in pressure during hypoxia, although with a few exceptions the increase in the pulmonary pressure gradient was not so striking as in the normal group. In some individuals, for no obvious reason, there was no pulmonary pressor response to hypoxia. In only two instances was there a significant increase in the cardiac output. As a rule the increase in the pulmonary vascular resistance was relatively lower than in the normal group. As a corollary of the slight change in the cardiac output, the peripheral vascular resistance tended to increase. While there were suggestive differences in some cases, no indisputably significant relocation of the pulmonary blood volume could be demonstrated.

It would appear that individuals with cardiopulmonary abnormalities are particularly vulnerable to hypoxia for two reasons. First, they may be unable to respond to local pulmonary disorders with effective pulmonary arteriolar constriction. Second, they are unable to maintain oxygen transport to the tissues by increasing cardiac output. This was apparent from the severity of the dyspnea caused by the experimental procedure. From the clinical standpoint these people are seriously jeopardized by the respiratory stresses of pulmonary embolization, atelectasis, pulmonary infection, heavy sedation, acute blood loss, high altitude and so forth. Thus, they can neither maintain arterial oxygen saturation by reducing blood flow through airless or poorly aerated lung nor compensate by increasing peripheral blood flow.

The observations reported here demonstrate that the pulmonary arteriocapillary pressure gradient can be strikingly increased without significant alterations in the pulmonary blood volume or the blood flow indicating a pulmonary vasoconstrictive mechanism. On the other hand, by the abrupt expansion of the blood volume without necessarily increasing the blood flow, a considerable increase in both the pulmonary arterial and the pulmonary capillary pressures can be produced without altering the pulmonary arteriocapillary pressure gradient.23 Under these circumstances the pulmonary vasculature apparently behaves as an elastic reservoir. With our present technics,
by neither maneuver is it possible to demonstrate a significant alteration in the pulmonary blood volume in relation to the general blood volume. It is apparent that pulmonary abnormalities in patients with heart disease represent a complex interrelationship between impaired myocardial function, pressure-volume factors, pulmonary vascular disease, vasomotor activity, impaired lymphatic drainage and other factors still unrecognized.

Summary and Conclusions

The acute circulatory reactions to short periods of hypoxia have been studied in eight normal individuals and in 12 individuals with cardiopulmonary dysfunction.

In the normal group, a rapid reduction in the arterial oxygen saturation to about 75 per cent caused a considerable increase in the pulmonary vascular resistance and in the cardiac output. The pulmonary capillary pressure was not altered.

In the abnormal group, a similar reduction in the arterial oxygen saturation caused a much smaller increase in the pulmonary vascular resistance and little or no increase in the cardiac output. The pulmonary capillary pressure was not altered. A few exceptions to this were noted. In contrast with the normal group, the inhalation of the low oxygen mixture caused severe dyspnea.

The most probable cause of the increase in the pulmonary arterial pressure during hypoxia is a direct effect of the low oxygen tension of the returning venous blood on the walls of the pulmonary arterioles. The increase in the cardiac output is a compensatory reaction, initiated by a fall in the peripheral vascular resistance, whereby oxygen transport to the tissues is maintained. In pulmonary disease these reactions may serve a useful purpose. In the presence of severe cardiopulmonary disease these reactions are impaired.

Definite evidence of alterations of the pulmonary blood volume during hypoxia could be demonstrated in neither the normal nor the abnormal group.

Acknowledgment

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References

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