Circulatory Adjustments to the Hypoxemia of Congenital Heart Disease of the Cyanotic Type

By Howard B. Burchell, M.D., Bowen E. Taylor, M.D., Julian R. B. Knutson, M.D., and Earl H. Wood, M.D., Ph.D.

In a limited number of subjects having hypoxemia related to congenital malformations of the heart, no evidence was obtained of a correlation between the degree of hypoxemia or the extent of the polycythemia and the systemic blood flow. The circulatory response to exercise was characterized by a greater increase in the arteriovenous oxygen difference than in the systemic blood flow. A syncopal reaction in one patient was preceded by a greatly increased systemic blood flow and a small arteriovenous oxygen difference.

Among individuals with cardiac malformations which permit venous arterial shunts, the oxygen saturation of arterial blood varies widely, but when such persons are in a good state of nutrition it usually is more than 70 per cent. This article is concerned with the circulatory adjustments to hypoxemia related to congenital heart disease. Particular mention will be made of two possible mechanisms that may maintain the oxygen saturation of arterial blood above a certain critical level. The first possibility is an increase in systemic blood flow and the second is an increase in the oxygen capacity of the blood. Both these mechanisms would allow higher oxygen saturations of venous blood, the first by a decrease in the difference in oxygen content of arterial and venous blood through increased blood flow, the second by producing a smaller decrease in the oxygen saturation of the venous blood. The latter includes the assumption that the arteriovenous oxygen difference remains the same. If the shunted venous blood is highly saturated with oxygen, it is apparent that the shunt will cause less decrease in the oxygen saturation of the arterial blood than would an equal quantity of venous blood which is less well saturated with oxygen. The systemic flow values represent the systemic cardiac output, with both ventricle contribut ing to the output in the presence of an intracardiac venous shunt. The percentage of venous blood shunted tends to remain constant in some cases, though in other cases, particularly during collapse reactions, the percentage of venous blood shunted (considered as a number of cubic centimeters of venous blood per 100 cc. of aortic flow) may be markedly increased. Further analysis of the factors responsible for the drop in arterial oxygen saturation with exercise constitutes the second purpose of this paper.

Methods

From the group of patients on whom venous catheterization of the heart has been performed in our laboratory, 20 subjects were selected who were in a good state of nutrition and who seemed to have accommodated themselves reasonably well to their intracardiac shunt and the consequent decreased tolerance to exercise. Individuals constantly unable to carry out mild activity were excluded as were those with extremely low arterial oxygen saturation. The majority of the patients were adults and none had shown any recent change in their compensation to their defect as judged by the history. None, however, could be said to have a normal tolerance to exercise.

The physiologic tests performed on each patient were in two parts, and a day or so intervened between the tests. The first was the exercise test in which the patient walked on a treadmill at 1.7 miles per hour, during which time the arterial oxygen saturation was measured by an ear oximeter and was also determined at intervals by manometric analysis of a sample of blood withdrawn with an indwelling arterial needle. Exercise was routinely continued for five minutes, unless the patient's tolerance to exercise did not permit him to continue as noted in table 1.
### Table 1.—Summary of Data in Twenty Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr.)</th>
<th>Clinical Diagnosis</th>
<th>Tolerance of Exercise</th>
<th>Surface Area (sq. M.)</th>
<th>B.M.R. %</th>
<th>O₂ Uptake (Ml. per Min. per sq. M.)</th>
<th>R.Q</th>
<th>Systemic Blood Flow (Liters per Min. per sq. M.)</th>
<th>O₂ Capacity (Vol. per 100 cc.)</th>
<th>Arterial O₂ Saturation (%)</th>
<th>Drop on Exercise (vol. per 100 cc.) (Resting)</th>
<th>A-V Difference (vol. per 100 cc.) (Resting)</th>
<th>Pressure P.A. (mm. Hg) (Resting)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Eisenmenger's complex</td>
<td>Fair</td>
<td>1.80</td>
<td>0</td>
<td>138</td>
<td>0.79</td>
<td>2.4</td>
<td>23.4</td>
<td>90</td>
<td>17</td>
<td>5.7</td>
<td>112/55</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>Eisenmenger's complex</td>
<td>Poor</td>
<td>1.82                +11*</td>
<td>153</td>
<td>0.84</td>
<td>2.5</td>
<td>22.6</td>
<td>90</td>
<td>15</td>
<td>6.2</td>
<td>117/52</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>Eisenmenger's complex</td>
<td>Fair</td>
<td>1.45                +45</td>
<td>172</td>
<td>0.94</td>
<td>3.3</td>
<td>21.8</td>
<td>80</td>
<td>21</td>
<td>5.2</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>4**</td>
<td>18</td>
<td>Eisenmenger's complex (?)</td>
<td>Poor</td>
<td>1.43                +6*</td>
<td>134</td>
<td>0.83</td>
<td>1.1</td>
<td>32.0</td>
<td>75</td>
<td>8**</td>
<td>11.7</td>
<td>11.7/52</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>Eisenmenger's complex</td>
<td>Fair</td>
<td>1.83                +10</td>
<td>135</td>
<td>0.83</td>
<td>3.5</td>
<td>22.4</td>
<td>83</td>
<td>15</td>
<td>3.9</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>6†</td>
<td>25</td>
<td>Isolated dextro cardia; septal defect</td>
<td>Fair</td>
<td>1.74                +22</td>
<td>169</td>
<td>0.79</td>
<td>4.3</td>
<td>16.0</td>
<td>86</td>
<td>33†</td>
<td>3.9</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>7‡</td>
<td>16</td>
<td>Isolated dextro cardia; septal defect</td>
<td>Fair</td>
<td>1.32                +17*</td>
<td>182</td>
<td>0.82</td>
<td>3.8</td>
<td>23.0</td>
<td>77</td>
<td>8‡</td>
<td>4.8</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>Isolated levo cardia; septal defect</td>
<td>Fair</td>
<td>1.58                +29</td>
<td>183</td>
<td>0.71</td>
<td>6.8</td>
<td>22.0</td>
<td>70</td>
<td>10</td>
<td>2.7</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>Eisenmenger's complex (?)</td>
<td>Good</td>
<td>1.27                +10*</td>
<td>173</td>
<td>0.93</td>
<td>4.9</td>
<td>26.2</td>
<td>78</td>
<td>38</td>
<td>3.5</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>31</td>
<td>Atrial septal defect</td>
<td>Fair</td>
<td>1.76                +28*</td>
<td>157</td>
<td>0.80</td>
<td>2.4</td>
<td>28.8</td>
<td>78</td>
<td>24</td>
<td>6.5</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>11§</td>
<td>35</td>
<td>Tricuspid atresia</td>
<td>Good</td>
<td>1.68                +23*</td>
<td>168</td>
<td>0.67</td>
<td>2.5</td>
<td>33.7</td>
<td>80</td>
<td>33</td>
<td>6.7</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>Tricuspid atresia</td>
<td>Fair</td>
<td>1.60                +20</td>
<td>169</td>
<td>0.76</td>
<td>3.4</td>
<td>25.3</td>
<td>79</td>
<td>20</td>
<td>5.0</td>
<td>114/67</td>
<td></td>
</tr>
<tr>
<td>13‖</td>
<td>16</td>
<td>Pulmonary stenosis; atrial septal defect</td>
<td>Poor</td>
<td>1.57                +11</td>
<td>176</td>
<td>0.77</td>
<td>3.5</td>
<td>27.8</td>
<td>63</td>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>14</td>
<td>18</td>
<td>Tetralogy of Fallot</td>
<td>Poor</td>
<td>1.38                +6</td>
<td>136</td>
<td>0.77</td>
<td>3.9</td>
<td>27.6</td>
<td>77</td>
<td>25</td>
<td>3.5</td>
<td>15/6/6</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>18</td>
<td>Tetralogy of Fallot</td>
<td>Fair</td>
<td>1.68                +2</td>
<td>155</td>
<td>0.75</td>
<td>4.2</td>
<td>33.5</td>
<td>75</td>
<td>34</td>
<td>3.7</td>
<td>15/6/6</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>Tetralogy of Fallot</td>
<td>Poor</td>
<td>0.97                +10*</td>
<td>200</td>
<td>0.73</td>
<td>6.9</td>
<td>26.2</td>
<td>78</td>
<td>30</td>
<td>2.9</td>
<td>15/6/6</td>
<td></td>
</tr>
<tr>
<td>17§</td>
<td>34</td>
<td>Tricuspid atresia</td>
<td>Good</td>
<td>1.63                +12</td>
<td>157</td>
<td>0.81</td>
<td>3.7</td>
<td>29.5</td>
<td>86</td>
<td>16</td>
<td>4.3</td>
<td>15/6/6</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>48</td>
<td>Ventricular septal defect</td>
<td>Fair</td>
<td>1.73                +26</td>
<td>163</td>
<td>0.78</td>
<td>2.5</td>
<td>25.4</td>
<td>95</td>
<td>11</td>
<td>6.5</td>
<td>15/6/6</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>15</td>
<td>Eisenmenger's complex</td>
<td>Fair</td>
<td>1.41                +3</td>
<td>165</td>
<td>0.78</td>
<td>2.9</td>
<td>30.6</td>
<td>79</td>
<td>29</td>
<td>5.7</td>
<td>15/6/6</td>
<td></td>
</tr>
<tr>
<td>20†</td>
<td>43</td>
<td>Eisenmenger's complex</td>
<td>Poor</td>
<td>1.79                +47</td>
<td>193</td>
<td>0.80</td>
<td>4.7</td>
<td>15.2</td>
<td>68</td>
<td>33†</td>
<td>4.1</td>
<td>132/44</td>
<td></td>
</tr>
</tbody>
</table>

Average 23.4

* Light breakfast.
** Patient unable to exercise more than two minutes.
† Recent pulmonary hemorrhages.
‡ Drop in saturation by standard oximeter only.
§ Some of the clinical and diagnostic features of Cases 11 and 17 have been discussed by Geraci, Dwy, and Burchell (Atrial Septal Defect and Probable Tricuspid Atresia in Adults, Proc. Staff Meet., Mayo Clin. 23: 510-516 [Oct. 27] 1948.)
‖ Patient unable to carry out exercise in laboratory.
The second part of the investigation consisted of cardiac catheterization after the method of Cournand and Ranges as modified by Wood and associates. All the tests were performed in the morning and many of the patients had had a light breakfast approximately two hours previously. The breakfast was allowed on the thesis that true basal states could not be obtained in any instance and as the procedure was primarily for diagnostic purposes, the patient would be more comfortable during the procedure if he ate breakfast. The oxygen saturation of arterial blood was determined throughout the procedure by a modified ear oximeter and samples obtained from the catheter were assayed for their oxygen saturation by means of the whole blood oximeter. These results were checked frequently against Van Slyke analyses.

Determinations of oxygen uptake were done by the collection and analysis of expired air in a metal gasometer and the metabolic rates were determined by the Mayo Foundation standards as discussed by Boothby, Berkson, and Dunn. The period of collection of the expired air in the resting state varied between five and ten minutes.

In 4 patients (Cases 17 to 20) an exercise test was carried out while the tip of the cardiac catheter was in the right atrium and samples representative of true mixed venous blood in the presence of intracardiac defects is a difficult one as interchamber mixing of blood may occur and samples from the superior and inferior vena cavae may show considerable difference (frequently 1 to 1.5 volume per 100 cc.) in their oxygen content. We attempted to minimize the difficulty by depending on the oxygen content of blood from the vena cava checking well with that of blood from the right atrium. Patients from whom adequate samples were not obtained were excluded from this series.

**Results**

The results are summarized in table 1. The patients as a rule had elevated metabolic rates. All of them, however, when resting were quiet.

### Table 2.—Circulation Measurements at Rest and Exercise in Selected Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (Yr.)</th>
<th>Diagnosis</th>
<th>Position</th>
<th>P O₂ Uptake (Ml. per Sq. M. per Min.)</th>
<th>RQ</th>
<th>Systemic Blood Flow, (LITERS per Sq. M. per Min.)</th>
<th>Arterial O₂ Saturation (per cent)</th>
<th>A-V O₂ Difference (Vol. per 100 cc.)</th>
<th>Resting O₂ Capacity (Vol. per 100 cc.)</th>
<th>Per cent Venous Blood Shunted</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>34</td>
<td>Tricuspid atresia</td>
<td>Supine</td>
<td>157</td>
<td>0.81</td>
<td>3.7</td>
<td>86</td>
<td>4.3</td>
<td>29.5</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standing</td>
<td>173</td>
<td>0.79</td>
<td>3.4</td>
<td>88</td>
<td>5.1</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Walking</td>
<td>331</td>
<td>0.84</td>
<td>4.4</td>
<td>70</td>
<td>7.3</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>48</td>
<td>Ventricular septal defect</td>
<td>Supine</td>
<td>163</td>
<td>0.78</td>
<td>2.5</td>
<td>95</td>
<td>6.5</td>
<td>25.4</td>
<td>10*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standing</td>
<td>168</td>
<td>0.79</td>
<td>2.2</td>
<td>95</td>
<td>7.7</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Walking</td>
<td>305</td>
<td>0.81</td>
<td>3.4</td>
<td>85</td>
<td>11.6</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>15</td>
<td>Eisenmenger's complex</td>
<td>Supine</td>
<td>165</td>
<td>0.78</td>
<td>2.9</td>
<td>79</td>
<td>5.7</td>
<td>30.6</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
<td>77</td>
<td>6.0</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Walking</td>
<td>372</td>
<td>0.94</td>
<td>3.8</td>
<td>48</td>
<td>9.8</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>43</td>
<td>Eisenmenger's complex</td>
<td>Supine</td>
<td>193</td>
<td>0.80</td>
<td>4.7</td>
<td>68</td>
<td>4.1</td>
<td>15.2</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Standing</td>
<td>210</td>
<td>0.76</td>
<td>3.8</td>
<td>61</td>
<td>5.6</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Walking</td>
<td>283</td>
<td>1.06</td>
<td>8.1</td>
<td>30</td>
<td>3.5</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

* See text for discussion of validity of calculation.
during the collection of the expired air and showed no overt signs of marked apprehension, and most had normal respiratory quotients.

In some patients with congenital intracardiac venous shunts we have observed that the oxygen saturation of arterial blood drops with exercise to a level which is characteristic for the individual (fig. 1), and the level may not be changed by increment in the work, namely, by increasing the rate of walking from 1.7 to 2.2 miles per hour.

![Diagram](http://circ.ahajournals.org/content/407/1/1619/F1.large.jpg)

Fig. 1.—The effect of exercise on the oxygen saturation of arterial blood in 2 of our patients (Cases 1 and 17) as measured by a modified oximeter reading and arterial samples. In Case 1, improvement during exercise followed the initial drop while in Case 17 the arterial saturation was maintained at a low level during exercise. Both patients show a characteristic transient drop in the arterial oxygen saturation on changing to the supine position following their exercise. This is believed to be related to a rapid return to the heart, when the supine position is resumed, of the desaturated blood pooled in the legs during the periods of standing.

The arterial saturation of blood during resting showed no definite correlation with the oxygen capacity of the blood (correlation coefficient -0.13) or the resting systemic flow (correlation coefficient -0.24) in this group of patients.

The drop in oxygen saturation of arterial blood on exercise showed no definite correlation to the arterial oxygen saturation during rest, the systemic flow during rest, or the oxygen capacity of the blood. The correlation coefficients being -0.37, +0.30, and +0.06, respectively.

The change in systemic flow related to exercise of 4 patients is shown in figure 2. None of these 4 patients showed the common manifestations of heart failure, that is, systemic or pulmonary congestion. They were comfortable at rest and their hearts were not grossly enlarged. The 3 patients (Cases 17, 18, and 19) who completed the five-minute period of exercise (walking 1.7 miles per hour on the treadmill) did so without obvious distress and the circulatory response was characterized by widening of the arteriovenous oxygen difference with little increase in systemic flow. The patient (Case 20) who was unable to continue walking showed an opposite response. The data in Case 18 is graphically portrayed (fig. 3) and the plateau levels of oxymoglobin of both the arterial and mixed venous blood are to be noted. The patient may be said to have been in a steady physiologic state during the exercise period. In contrast, the results in Case 20 (fig. 4) show a progressive decrease in arterial saturation without evidence of equilibrium being established, and this was associated with progressive deterioration in the clinical state of the patient and finally with collapse.

**Comment**

All of these patients had a varied degree of disability, and, though free of edema or dyspnea at rest, could be said to have inadequate circulation under conditions of exercise. The symptoms that appeared in some patients, either singly or together, were exhaustion, weakness, faintness or dyspnea.

The results of the metabolic rates were equivalent to those we could expect in a group.
of normal subjects under resting but nonbasal conditions. These patients presented no evidence of reduced tissue metabolism such as has been claimed by Bing and co-workers\(^8\) to occur in more severely hypoxic children with congenital heart disease. The results in our group are in accord with the observations of Houston and Riley\(^9\) on individuals during acclimatization to low barometric pressure who showed no change in their oxygen consumption under conditions of rest and standard exercise at low pressure. Similar results were obtained by Douglas and co-workers,\(^10\) on frequent studies of oxygen consumption performed under conditions of rest and during exercise before and after ascent to Pike's Peak. The figures for the oxygen uptake at near sea level and at all-tide were remarkably uniform. Similar uniform results in the oxygen uptake in 2 subjects at low and high altitude were obtained by Grollman.\(^11\)

The average systemic blood flow of our 20 patients was slightly above the average normal as reported by Stead and his co-workers\(^12\);

![Graph](https://example.com/graph.png)

**Fig. 2.—**The effect of exercise on the systemic blood flow and oxygen consumption in 4 patients discussed in the text. The oxygen saturations of arterial blood in Case 17 dropped from 86 to 70 percent on exercise; in Case 18 from 95 to 65 percent; in Case 19 from 79 to 48 percent and in Patient 20 from 61 to 39 percent. In Case 20 a physiologic steady state was never present and exercise lasted only a minute and a half. The dotted lines represent the border of normal responses and were constructed by finding boundaries that would enclose the charted results obtained for 3 normal persons by Riley and his co-workers\(^13\) and for 7 normal persons by Hickam and Cargill.\(^14\) Subject 5 of the latter investigators was excluded as the results for this subject differed so radically from those of the other subjects.

and the lowest and highest values are definitely outside the normal range. However, Stead and his associates found the average index to be 3.3 for the composed subject as compared to 5.5 for the anxious one. Bing and co-workers' likewise have found wide variation in the systemic flows of their cyanotic patients; the values in their cases, expressed as liters per minute per square meter of body surface, ranged from 0.90 to 11.40. In their group of 5 patients with the
Fig. 3.—The effect of walking on the oxygen saturation of arterial and venous blood and the systemic blood flow in a patient with congenital heart disease (Case 18).

Fig. 4.—The effect of walking on the oxygen saturation of arterial and venous blood and systemic blood flow in a patient with congenital heart disease (Case 20).
Eisenmenger complex, Bing and his associates\textsuperscript{13} found the systemic flow to be at low normal values (average 2.7).

The maintenance of a favorable minimal oxygen saturation of arterial blood in cases of pulmonary arteriovenous fistulas through an increased systemic blood flow was suggested as a possibility by Burchell and Clagett.\textsuperscript{14} Actual determinations on this type of case are rare but the flow may be of normal value as in the case of Maier and associates\textsuperscript{15} or increased as in the cases of Baer\textsuperscript{16} and of Baker and Trounce.\textsuperscript{17}

Extensive investigations have been carried out at high altitude concerning the effect of the hypoxemia on cardiac output. The fairly recent work of Asmussen and Consolazio\textsuperscript{18} on Mount Evans is in general agreement with that of Grollman\textsuperscript{19} on Pike's Peak in indicating that an increased circulation rate (increased systemic flow) occurred early in the acclimatization period. Grollman, from observations on hypoxia produced by mixtures of oxygen and nitrogen, concluded that the stimulus came at rather specific hypoxic levels, that is, when the oxygen in the inspired mixture dropped to 11.6 per cent. Such a stimulus threshold was supported by observations of Asmussen and Chiodi,\textsuperscript{19} who found that the oxygen in the inspired air had to be low enough to reduce the arterial oxyhemoglobin to 70 to 80 per cent of normal in order to produce an increase in the cardiac output. In individuals acclimatized to low barometric pressure in a low pressure chamber for several days, Houston and Riley\textsuperscript{9} found an increased cardiac output as one of the less significant compensatory mechanisms.

It is of interest that the 2 patients who had severe syncopal reactions on exercise showed a markedly different circulatory pattern prior to exercise. The one (Case 4) had an extremely low systemic flow (1.1 liters per minute per square meter), a big arteriovenous oxygen difference at rest, and prior to the faintness showed only a minor drop in arterial oxygen saturation on exercise. The other (Case 20) had a high systemic flow and a narrow arteriovenous oxygen difference at rest, and prior to faintness showed a marked drop in arterial oxygen saturation on exercise. In this latter case the respiratory quotient corresponding to oxygen consumption during the exercise was 1.06 (table 2). This is possibly related to the fact that the period of oxygen uptake was allowed to extend past the time that the patient was actually walking, though he was still standing in place on the treadmill. During the latter part of the collection period for expired air, excess carbon dioxide was being lost. However, the exercise alone might have been responsible.\textsuperscript{10} The mixed venous and arterial oxygen saturations were reasonably steady during this period and the systemic flow value obtained probably has a validity in reflecting a high systemic flow. Such a presyncopal high systemic blood flow in a severely hypoxic condition would suggest a reaction analogous to that observed by Anderson and associates\textsuperscript{20} in which high blood flows were obtained in muscle in the induced hypoxic state prior to syncope. In their subjects, bradycardia was a characteristic finding; in our patient, persistent tachycardia was recorded throughout the procedure by a cardiotachometer.

In the circulatory collapse in normal subjects associated with anxiety, observed by Hickam and associates,\textsuperscript{21} the cardiac output either dropped slightly or remained the same and similar results were reported by Warren and colleagues.\textsuperscript{22} The latter also mentioned the marked slowing of the pulse rate. Barcroft and his co-workers,\textsuperscript{23} in studies on posthemorrhagic fainting, observed small decreases in the cardiac output inadequate to explain the fainting. None of these investigative groups stressed the technical difficulties, namely, obtaining a well-fitting mask or mouthpiece and an adequate period of a minute or more, that have been of concern to us in the measurement of the oxygen uptake in the subject bordering on a collapse state.

Extremely important in any consideration of hypoxemia is the possibility that this condition may be self-aggravating through increased pulmonary resistance to blood flow. Riley and associates\textsuperscript{24} noted that those patients who had pulmonary disease and whose arterial oxyhemoglobin dropped significantly during exercise were the ones whose pulmonary arterial pressures were highest during exercise. These workers questioned whether the elevation of
pressure in the pulmonary artery might be related at least in part to the associated anoxia. They stated that such a possibility was given some general support from the observation of Motley and associates that in normal subjects the pressure in the pulmonary arteries rose with the breathing of 10 per cent oxygen, and from the experiments of von Euler and Liljestrand on cats in which there was a constant decrease in the pressure in the pulmonary artery on administration of 100 per cent oxygen and an increase on administration of 10 per cent oxygen in nitrogen. Von Euler and Liljestrand concluded from their experiments that the regulation of pulmonary blood flow was mainly mediated by local action of the blood and alveolar gases.

In a case of venous arterial shunt it might be assumed that an increase in pulmonary vascular resistance would cause an increase in the venous shunt and a further decrease in the percentage of arterial oxyhemoglobin. With the increased hypoxemia with exercise it is possible that a reciprocating aggravation of the hypoxic state might occur in which both factors, the hypoxemia and pulmonary resistance, might propagate each other. We have no observations which support such a thesis and have some observations in 3 cases in which such a phenomenon did not occur, the shunt remaining constant with exercise. Our calculations concerning the venous shunt in these patients when 10 to 14 per cent and 100 per cent oxygen were administered do not reveal uniform results. In one patient a decreased venous shunt on the administration of 100 per cent oxygen apparently occurred; in others, the shunt remained the same. One patient (Case 17) of this group has been studied at frequent intervals for two years. He has breathed 8 per cent oxygen for five to six minutes without distress on a number of occasions and has exercised for five minutes (walking 1.7 miles per hour on a treadmill) while breathing 12 per cent oxygen without discomfort. Case 19 is of particular interest in that the arterial oxygen saturation decreased with exercise through the range wherein one might expect, from the work on hypoxic states of normal persons, that the cardiac output might be stimulated. There seems no evidence of this having occurred (fig. 5). Patient 20 of the series was probably the most hypoxic patient and the percentage of venous blood shunted was unchanged by breathing 100 per cent oxygen, being calculated as 47 per cent. From these early observations, the conclusion seems probable that in patients who have congenital heart disease the total pulmonary vascular resistance bears no con-

![Fig. 5.—The effect of breathing various percentages of oxygen and of exercise on the oxygen saturation of arterial blood in a patient with congenital heart disease. The values charted represent those obtained by Van Slyke analyses of samples of blood drawn from the radial artery. The blood was taken with an indwelling arterial needle at the time when the ear oximeter showed that a plateau of arterial saturation had been established. This patient was also able to carry out the exercise test, walking 1.7 miles per hour on a power driven treadmill, breathing 12 per cent oxygen (Case 17).](image-url)
capacities of 15 and 16 cc. per 100 cc.) related to recurring pulmonary hemorrhages, we could not be certain of a clinically suspected increased disability. The oxygen capacity of the blood in Patient 17 had been reduced from 34 to 21 volumes per 100 cc. by phlebotomies without reduction in tolerance to exercise but with a moderate, perhaps unrelated, decrease in arterial saturation during rest. Likewise, due to variability between persons of this group, it would be unwise to draw any conclusions from the apparent possibility of slight inverse correlation between the oxygen capacity and the systemic blood flow.

It is of interest that Asmussen and Consolazio stated that the drop in cardiac output after its initial rise at altitude was probably related to the development of polycythemia. As yet, evidence that polycythemia has a relationship to cardiac output is not convincing; for instance, all the early work as reviewed by Grollman on polycythemia vera indicated that the cardiac output in this condition was normal.

The drop in oxygen saturation of arterial blood with standard exercise has shown no infallible correlation to the physiologic variables studied in this group nor with the general clinical impression of the individual's disability. However, as previously mentioned, the severely cyanotic children with extremely low oxygen saturation of arterial blood on exercise were not included.

The circulatory changes of 3 patients during exercise were similar to those of Hickam and Cargill's patients with acquired heart disease who had congestive heart failure; that is, little increase in output with a large increase in the arteriovenous oxygen difference. It needs hardly be mentioned that even though the reaction is abnormal, it represents an increase in efficiency of the oxygen transport system. The fourth patient studied, already discussed in relation to the syncopal reaction, showed an increase in systemic blood flow with a narrow arteriovenous oxygen difference. In respect to the other 3 patients referred to, it is believed that they were in a relatively steady state during the exercise. In Case 18, serial samplings of expired air showed a close agreement in the oxygen uptake. It is of interest too that the increment in oxygen uptake of these 3 patients when walking at 1.7 miles per hour was in general agreement with the observations of Douglas and his associates, who found the oxygen consumption was increased by a factor of 2.7 when subjects walked at 2 miles per hour. It may be noted that in Cases 18, 19, and 20 the percentage of venous blood shunted increased on exercise. The greatest increment in the shunt was in Case 20. The validity of the determinations of the percentage of venous blood shunted in these patients is dependent on the assumption that the pulmonary venous blood was normally saturated and remained so with exercise. The calculations were made after the method of Burchell and Wood.

The arterial oxygen saturation under conditions of rest in Case 18 varied on two different days from 91 to 95 per cent. The calculation of any small shunt present is fraught with possible error. Breathing 100 per cent oxygen, this patient's arterial saturation was 100 per cent, and there were 1.6 cc. of excess oxygen in solution per 100 cc. of blood. At this time we could say no shunt was present. With exercise the arterial saturation abruptly decreased to 85 per cent and the calculated percentage of venous blood shunted was 22. It may be mentioned that a decrease of this magnitude in the oxygen saturation of arterial blood has been observed by us occasionally in patients with pulmonary congestion and with severe pulmonary disease, but this observation is opposite to the usual rule. In a previous publication, two of us reported the tendency of 2 patients, one of whom was Case 17, to maintain the same relative percentage of shunt under varying conditions. These further observations on additional patients indicate that an increase in the shunt may be an important contributing factor to the fall in arterial oxygen saturation under some conditions.

Summary and Conclusions

In the group of patients with cyanotic congenital heart disease no correlations could be definitely established between the circulation rate (systemic flow) and the oxygen saturation or the oxygen capacity of arterial blood. The group was heterogenous in respect to age,
anatomic defect, and clinical disability. A threshold value below which the oxygen tension of arterial blood acted as a stimulus for an increase in systemic flow was not established in these cases.

The drop in arterial oxygen saturation on standard exercise showed no definite correlation to oxygen saturation of arterial blood or systemic flow during rest, to the oxygen capacity, or to the general clinical history.

It was apparent that polycythemia was not a uniformly necessary requirement for the well-being of the hypoxic patient suffering from congenital heart disease of the cyanotic type.

The dynamics of the circulation of 3 patients completing a standard exercise test resembled that reported in the literature as characteristic of persons in heart failure, that is, the increased oxygen transport was related more to an increased arteriovenous difference than to increased cardiac output.

One individual, unable to continue exercise, whom we observed in the presyncopal state showed a great increase in the shunt of venous blood, a high systemic blood flow, tachycardia, and severe hypoxemia.

No evidence was obtained that increasing hypoxia caused increased pulmonary resistance in the special cases studied. This possibility has not been excluded in the other cases.

REFERENCES


16 Baker, S.: Personal communication.


20 Anderson, D. P., Allen, W. J., Barcroft, H., Edholm, O. G., and Manning, G. W.: Cir-
CIRCULATORY ADJUSTMENTS TO HYPOXEMIA


Circulatory Adjustments to the Hypoxemia of Congenital Heart Disease of the Cyanotic Type
HOWARD B. BURCHELL, BOWEN E. TAYLOR, JULIAN R. B. KNUTSON and EARL H. WOOD

Circulation. 1950;1:404-414
doi: 10.1161/01.CIR.1.3.404

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1950 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/1/3/404

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/