Hemodynamic Responses to Oxygen Breathing in Children with Severe Anemia

By Gerd J. A. Cropp, M.D., Ph.D.

SUMMARY

Hemodynamic responses to 100% oxygen inhalation were examined in seven anemic children (hemoglobin 1.9 to 3.8 g/100 ml; hematocrit 9 to 14%). During air breathing mean values for cardiac index were 7.71 L/min/m², for heart rate 129/min, for stroke index 61.7 ml/m², and for systemic vascular resistance 11.5 R.U. Oxygen administration significantly decreased mean values of cardiac index to 6.61 L/min/m², of heart rate to 119/min and of stroke index to 56.6 ml/m², and increased mean systemic vascular resistance to 14.2 R.U. Oxygen breathing raised systemic oxygen content 23% and oxygen transport 5%, despite decreases in cardiac output. Since oxygen breathing did not change the hematocrit (and thus viscosity), the increase in vascular resistance indicates active vasoconstriction. It is postulated that in anemia tissue hypoxia causes vasodilation of systemic resistance vessels. When anemia is not severe, baroreceptor reflexes prevent significant reductions in blood pressure and systemic vascular resistance by compensatory, neurogenic vasoconstriction. When anemia becomes severe and vasodilation extreme, blood pressure is maintained by an increase in cardiac output. Cardiac output is elevated by decreased vagal inhibition and increased myocardial contractility, which cause tachycardia and increased stroke volumes respectively.

Additional Indexing Words:
Systemic vascular resistance  
Blood viscosity  
Heart rate  
Hematocrit  
Autoregulation of blood flow  
Cardiac output  
Stroke volume

IN ANEMIA the oxygen content of systemic arterial blood is low and oxygen transport to the tissues is reduced. Under these conditions the oxygen requirements of the body are satisfied firstly by more complete extraction of oxygen from the blood and secondly by an increase in cardiac output. When the hemoglobin concentration falls below 7 g/100 ml of blood, the cardiac output begins to increase, and the cardiac index reaches approximately 8 L/min/m², when the hemoglobin levels have fallen to 3 to 3.5 g/100 ml.¹-³

Observations in normal man have shown that oxygen breathing reduces heart rate and cardiac output, and increases systemic vascular resistance.⁴-⁶ In anemic subjects the cerebral vascular resistance is also increased by oxygen administration.⁷ Although inhalation of 100% oxygen did not reduce the cardiac output in anemic dogs,⁸ we thought that the effects of oxygen administration should be investigated in severely anemic, unanaesthetized human subjects, to determine whether their hemodynamic and clinical distress could be lessened by this form of therapy.

Methods

Hemodynamic studies were performed on seven boys, referred to us for treatment of their severe anemias. The case material is described in table 1. All anemic children were dangerously ill (hemoglobin 1.9 to 3.8 g/100 ml; hematocrit 9 to 14%). Six children were suffering from associated diseases besides their anemia, and their serious clinical state led to the decision to treat these children by isovolumetric exchange transfusions,⁹ rather than by simple transfusions or iron...
therapy. The preparation for exchange transfusion required the insertion of arterial and venous catheters by sterile surgical technic under local anesthesia. The presence of these catheters permitted the performance of hemodynamic studies without further discomfort to the patients. The technic of vessel cannulation and additional clinical information on each of these patients have been given previously.3 One child (case 2) was sedated prior to the cannulation of the vessels (meperidine hydrochloride 15 mg im, promethazine hydrochloride 7 mg im); the other children received no premedication. During the execution of the studies the children were observed closely for any signs of distress. The protocol was explained to the patients (when old enough) and to the parents of the children. A written consent was obtained from all parents prior to the study and the exchange transfusions.

Cardiac outputs were measured by the dye-dilution technic. Indocyanine green dye (Hynson, Westcott and Dunning, Inc., Baltimore, Maryland) was injected into the venous catheter and its connector; the tip of this catheter was located in the superior vena cava. The dye was flushed into the circulation by rinsing the catheter with normal saline. Systemic arterial blood was withdrawn at a rate of 19 ml/min with a Harvard infusion-withdrawal pump (Harvard Apparatus Co., Dover, Massachusetts) from a catheter in the brachial artery. The arterial blood passed through a sterilized densitometer cuvette (Gilson Medical Electronics, Middleton, Wisconsin) into a sterile, heparinized syringe. The withdrawn blood was returned to the patient as soon as the dye curve was recorded. A dye curve was inscribed on the servo-channel of the Gilson recorder or on a potentiometric recorder (Heath Co., Benton Harbor, Michigan). The primary circulation of dye was determined by the method of Kinsman and associates.10 The area under the curve, describing the first circulation of dye, was measured with a planimeter. The densitometer was calibrated with anemic blood, and care was taken that peak dye concentrations did not exceed 15 mg/L; below this dye concentration the monochromatic densitometer responded approximately linearly to increases in dye concentrations.11 The cardiac outputs were expressed as cardiac indices (L/min/m²); surface areas were calculated from the nomograms of Sendroy and Cecchini12 for small children, and of DuBois and DuBois13 for older children. Stroke indices were calculated from cardiac indices and heart rates. Heart rates were obtained by counting the arterial blood pressure signals for periods of 20 to 30 seconds on the records. Systemic arterial pressures were measured through the arterial catheter with a Statham strain gauge (P23 Db) and recorded on a Gilson recorder. Mean arterial pressures were approximated by an approximating equation14:

\[
\text{Mean arterial pressure} = \text{diastolic pressure} + \frac{1}{3} \text{pulse pressure.}
\]

### Table 1

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Hb (g/100 ml)</th>
<th>Het (%)</th>
<th>Cause of anemia</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 yr, 3 mo</td>
<td>7.5</td>
<td>1.9</td>
<td>9</td>
<td>Fe-deficiency; nutritional</td>
<td>Heart failure, pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>1 yr, 8 mo</td>
<td>12.5</td>
<td>3.2</td>
<td>13</td>
<td>Fe-deficiency, nutritional</td>
<td>Fatigue, irritability, anorexia</td>
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<tr>
<td>3</td>
<td>7 mo</td>
<td>8.2</td>
<td>3.7</td>
<td>13</td>
<td>Fe-deficiency, blood loss at birth</td>
<td>Bronchiolitis, fatigue</td>
</tr>
<tr>
<td>4</td>
<td>10 mo</td>
<td>8.3</td>
<td>3.2</td>
<td>14</td>
<td>Fe-deficiency, nutritional</td>
<td>Gastritis, fatigue</td>
</tr>
<tr>
<td>5</td>
<td>13 yr, 12 mo</td>
<td>22.1</td>
<td>3.8</td>
<td>10</td>
<td>Renal disease, repeated nose bleeds</td>
<td>Early heart failure, renal failure</td>
</tr>
<tr>
<td>6</td>
<td>10 yr, 4 mo</td>
<td>18.7</td>
<td>3.8</td>
<td>10</td>
<td>Renal disease</td>
<td>Digitalis intoxication, renal failure</td>
</tr>
<tr>
<td>7</td>
<td>2 yr, 10 mo</td>
<td>9.4</td>
<td>3.6</td>
<td>11</td>
<td>Renal disease, repeated nose bleeds</td>
<td>Renal failure, hypertension</td>
</tr>
</tbody>
</table>

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Total systemic vascular resistance was calculated from the mean arterial pressure (mm Hg) and the cardiac index (L/min/m²) and was expressed in resistance units (R.U. = mean pressure/cardiac index).

Arterial blood gases and pH measurements were made on 0.5 to 1 ml samples. The specimens were analyzed within 2 minutes of collection on radiometer electrodes (Copenhagen, Denmark). Measurements of blood gas tensions and pH were adjusted to the patient's body temperature. Temperature corrections and hemoglobin oxygen saturations were computed with the Severinghaus blood gas calculator, taking into account existing hemoglobin concentrations.

The children had rested for at least 15 minutes after completion of the vessel cannulation and before any measurements of hemodynamic parameters were begun. With the children breathing room air (mean PaO₂ at Denver = 131 mm Hg) and resting comfortably, blood specimens were collected from the arterial catheter for the determination of hemoglobin concentrations (cyanmethemoglobin method), hematocrit, blood gases, and pH. Following this, we recorded blood pressures and a dye curve. The patients then breathed oxygen. Oxygen was administered at a rate of 10 to 12 L/min. The excess gas escaped through the head hole at a rate of 10 to 12 L/min. The rate of oxygen flow was sufficient to prevent the buildup of carbon dioxide inside the hood. The administration of oxygen by hood was tolerated well by children of all ages. One child (case 5) breathed oxygen from a face mask. Measurements of blood gases, blood pressure, and cardiac output were repeated after 10 to 15 minutes of oxygen breathing. After hemodynamic measurements in the anemic state during air and oxygen breathing had been completed, the children were exchange-transfused.

**Results**

**Blood Gases, Arterial Saturations, and pH Measurements**

Measurements of arterial PaO₂, PaCO₂, pH, and calculated values for oxygen saturations of hemoglobin during air and oxygen breathing are summarized in table 2. It can be seen that all anemic patients hyperventilated during air and oxygen breathing as indicated by the low PaCO₂ values, and relatively high arterial oxygen tensions and saturations for Denver altitude in six of seven patients. Normal mean adult values for Denver are: PaCO₂ 36 mm Hg, PaO₂ 69 mm Hg; pH 7.42, oxygen saturation 94%. The data indicate that children with iron-deficiency anemia were in a state of compensated metabolic acidosis. Three children with chronic renal disease had severe uncompensated metabolic acidosis. The administration of oxygen raised mean PaO₂ from 87 to 371 mm Hg, hemoglobin saturations to 100%, and arterial pH by 0.05 unit. All increases were statistically significant.

**Table 2**

*Arterial Blood Gases, Saturations, and pH Values*

<table>
<thead>
<tr>
<th>Case no.</th>
<th>PaO₂ (mm Hg)</th>
<th>O₂ Saturations (%)</th>
<th>PaCO₂ (mm Hg)</th>
<th>pH</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Air</td>
<td>O₂</td>
<td>Air</td>
<td>O₂</td>
</tr>
<tr>
<td>1</td>
<td>101</td>
<td>390</td>
<td>98</td>
<td>100</td>
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<tr>
<td>2</td>
<td>66</td>
<td>340</td>
<td>93</td>
<td>100</td>
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<td>81</td>
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<td>4</td>
<td>80</td>
<td>450</td>
<td>97</td>
<td>100</td>
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<tr>
<td>5</td>
<td>100</td>
<td>230*</td>
<td>96</td>
<td>100</td>
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<tr>
<td>6</td>
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<td>7</td>
<td>92</td>
<td>405</td>
<td>97</td>
<td>100</td>
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<tr>
<td>Mean</td>
<td>87</td>
<td>371</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>±SD</td>
<td>11.4</td>
<td>68.0</td>
<td>1.55</td>
<td>0.0</td>
</tr>
<tr>
<td>±SE</td>
<td>4.7</td>
<td>27.8</td>
<td>0.63</td>
<td>0.0</td>
</tr>
<tr>
<td>Sig. of change (P-value)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>ns†</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* O₂ administered by mask.
† NS = not significant.
Table 3

Cardiac Indices, Heart Rates, and Stroke Indices

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Cardiac index (L/min/m²)</th>
<th>Heart rate/min</th>
<th>Stroke index (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air</td>
<td>O₂</td>
<td>Air</td>
</tr>
<tr>
<td>1</td>
<td>9.50</td>
<td>8.23</td>
<td>140</td>
</tr>
<tr>
<td>2</td>
<td>9.82</td>
<td>8.45</td>
<td>160</td>
</tr>
<tr>
<td>3</td>
<td>6.72</td>
<td>5.84</td>
<td>148</td>
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<td>4</td>
<td>8.05</td>
<td>6.26</td>
<td>144</td>
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<td>5</td>
<td>7.07</td>
<td>6.95</td>
<td>120</td>
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<td>6</td>
<td>6.62</td>
<td>5.64</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>6.21</td>
<td>4.91</td>
<td>112</td>
</tr>
<tr>
<td>Mean</td>
<td>7.71</td>
<td>6.61</td>
<td>129</td>
</tr>
<tr>
<td>±SD</td>
<td>1.34</td>
<td>1.24</td>
<td>26.3</td>
</tr>
<tr>
<td>±SE</td>
<td>0.55</td>
<td>0.50</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Sig. of change (P-value) <0.005 <0.05 <0.05

One hundred milliliters of blood can physically dissolve 0.003 ml of oxygen at a partial pressure of 1 mm Hg; if 1 g hemoglobin binds 1.36 ml oxygen, and hemoglobin is 96% saturated, as in our subjects during air breathing (mean PAo₂ = 87 mm Hg, pH 7.30, the total oxygen content of the anemic blood (mean hemoglobin concentration 3.3 g/100 ml) would be 4.57 ml oxygen/100 ml blood (4.31 ml oxygen/100 ml blood hemoglobin bound, 0.26 ml oxygen/100 ml blood in solution). During oxygen inhalation hemoglobin was fully saturated (4.49 ml oxygen/100 ml blood hemoglobin bound), more oxygen was in solution (1.11 oxygen/100 ml blood in solution), and the total oxygen content was 5.60 ml oxygen/100 ml blood. The administration of oxygen, therefore, raised the total oxygen content of blood, on the average, by 23%.

Cardiac Indices, Heart Rates, and Stroke Indices

During air breathing, cardiac indices, heart rates, and stroke indices were elevated in the anemic children to levels seen in older children or adults with equally severe anemia. The administration of oxygen significantly reduced all these measurements as can be seen in table 3 and figure 1. All changes were statistically significant. Oxygen breathing decreased the mean cardiac index from 7.71 to 6.61 L/min/m² (14%), mean heart rate from 129 to 119/min (7.8%), and the mean stroke index from 61.7 to 56.6 ml/m² (8.3%).

Figure 1

Mean values (±SE) of cardiac index, heart rate, and stroke index in anemic children during air and oxygen breathing. Oxygen inhalation decreased all parameters significantly.

Blood Pressures and Systemic Vascular Resistances

The effects of oxygen breathing on systolic and diastolic pressures and systemic vascular resistance are presented in table 4 and figure 2. Although systemic blood pressures tended to increase during oxygen breathing, these changes were not statistically significant. Peripheral vascular resistance increased significantly from 11.46 to 14.18 R.U. or by 24%.

Discussion

The observations on seven severely anemic children have shown that the administration of oxygen increased oxygen delivery to the
tissues and lessened the work of the heart. Calculations based on our data indicate that the oxygen transport to the tissues (cardiac index times total systemic arterial oxygen content) increased by 5% during oxygen breathing, despite a reduction in cardiac index of 14%. It is probable that the benefits of oxygen breathing will be greatest when anemia is severe; the extra amount of oxygen that can be put into solution by breathing 100% oxygen approximately equals the oxygen carried by 1 g of hemoglobin, or oxygen administration can increase the total oxygen content of systemic arterial blood by 25 to 35% when the hemoglobin level is below 4 g/100 ml blood. The benefits of oxygen administration are also likely to be greater in Denver (altitude 5,300 feet) than at sea level, since at this altitude during air breathing, hemoglobin is less saturated with oxygen than at sea level. Our observations provide quantitative evidence that oxygen can give useful short-term support to the seriously ill and anemic child, until the anemia can be corrected. Because of the toxic effects of prolonged oxygen administration, oxygen therapy can only be of temporary value.

Oxygen administration increased the peripheral vascular resistance in anemic children without changing blood hematocrit or blood viscosity. Hematocrit and the total cross-sectional area of the resistance vessels are the only two variables likely to affect vascular resistance in anemia. Since hematocrit stayed constant, vasoconstriction must have been responsible for the increase in vascular resistance during the inhalation of oxygen. Many investigators have shown that a decrease in oxygen content of the blood perfusing a tissue will lead to vasodilation; this hypoxia-induced vasodilation is independent of innervation and is an important factor in the autoregulation of tissue perfusion.
Figure 3

Hypothetical schema of the control of central systemic blood pressure and cardiac output in severe anemia.

It is postulated that in anemia tissue hypoxia causes vasodilation, which lowers resistance to blood flow and systemic arterial blood pressure (fig. 3). The fall in blood pressure stimulates baroreceptors, which elicit compensatory neurogenic vasoconstriction; thus arterial pressure and peripheral vascular resistance are maintained at nearly normal levels. In the proposed control system, systemic arterial pressure is the "controlled variable" and baroreceptors are the principal sensors. When anemia becomes severe (hemoglobin concentration less than 7 g/100 ml), tissue hypoxia becomes so marked that baroreceptor reflexes cannot maintain sufficient vasomotor tone to maintain systemic pressure. Under these circumstances blood pressure can be kept up only by increases in cardiac output. It is postulated that the increase in cardiac output is brought about by a decrease in vagal inhibition and stimulation of the myocardium, probably by epinephrine and sympathetic nerves. These mechanisms lead to tachycardia and an increase in stroke volume. The neural influences on the heart are probably triggered by baroreceptor reflexes as blood pressure tends to fall secondary to progressive tissue hypoxia. Oxygen breathing increased systemic arterial oxygen content 23%, which lessened the hypoxia-induced vasodilation, as indicated by a 24% rise in calculated peripheral resistance. The effectiveness of the negative feedback control system is apparent when one notes that oxygen administration increased oxygen transport by 5%, despite a reduction in the cardiac index of 14%. It is typical of negative feedback systems that the "controlled variable" (in anemia: systemic blood pressure) is not perfectly maintained. In anemia mean and diastolic pressures are low, and oxygen breathing tended to elevate the pressure slightly. When tissue hypoxia and vasodilation become extreme, central blood pressure cannot be maintained by vasomotor or humoral mechanisms, and high output failure will develop.

The reduction of cardiac output by oxygen breathing in our anemic children does not agree with the findings of Murray8 in dogs. In Murray's experiments the animals were anesthetized and may, therefore, not have been in a state comparable to our chronically anemic children. Murray and associates8, 24-26 concluded from these and other studies that the viscosity of blood was the principal determinant in the control of cardiac output in anemia. An examination of the relation between viscosity of blood and hematocrit27, 28 points out that the viscosity changes less when the hematocrit rises from 10 to 20%, than when it rises from 20 to 40%; nevertheless, it is in the hematocrit range of 10 to 20% that the major changes in cardiac output occur in anemia, with essentially no increases in cardiac output at hematocrits above 25%. In view of these considerations and our observations that oxygen administration can lower cardiac output without altering the hematocrit, we conclude that the low blood viscosity is not a primary factor in the control of cardiac output in anemia.

Conclusions

1. Oxygen therapy may provide short-term support for seriously ill, anemic children, until
the hemoglobin deficit can be corrected more permanently.

2. Oxygen breathing reduced the cardiac index, heart rate, and stroke volume in severely anemic children.

3. Oxygen breathing did not alter hemato-crit (or viscosity) of blood and, therefore, increased systemic vascular resistance by active vasoconstriction.

4. Oxygen inhalation increased oxygen transport by 5%, despite a 14% decrease in cardiac index.

5. It is proposed that vasomotor tone and cardiac output in anemia are regulated to keep systemic blood pressure at adequate levels and that baroreceptors and humoral factors are important in this regulation.

Acknowledgment

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