Decreased Affinity of Blood for Oxygen in Patients with Low-Output Heart Failure

By James Metcalfe, M.D., Dharam S. Dhindsa, Ph.D., Miles J. Edwards, M.D., and Athanasios Mourdjinis, M.D.

ABSTRACT

Oxygen affinity of blood was measured in 16 patients (nonsmokers) without anemia and with clinical evidence of low cardiac output. Of these patients, 12 were catheterized and showed an arteriovenous oxygen concentration difference across the lungs greater than 5 ml/100 ml. The partial pressure of oxygen required to half-saturate their blood with oxygen (P<sub>50</sub>) averaged 29.4 mm Hg (sd ± 1.9). Blood from normal subjects (nonsmokers) had an average P<sub>50</sub> of 27.3 mm Hg (sd ± 0.9). The decreased oxygen affinity found in blood of patients with low levels of cardiac output is considered as a compensatory adjustment to poor tissue blood flow, promoting the diffusion of oxygen from blood to tissue capillaries to intracellular sites of utilization.

ADDITIONAL KEY WORDS

compensation for tissue hypoxia oxygen dissociation curve

A decreased affinity for oxygen has been demonstrated in blood from patients with varied conditions including high altitude exposure (1-3), anemia of several different etiologies (4-9), and arterial hypoxemia due to either congenital heart disease or chronic obstructive pulmonary disease (10). One physiological common denominator of these clinically dissimilar entities is an impairment in the delivery of oxygen to tissues which is reflected by a lowered oxygen tension in venous blood leaving the tissues (11).

Tissue blood flow is, of course, an important link in the chain of oxygen supply which runs from the environmental air to the mitochondria. Patients with abnormally low levels of cardiac output and decreased peripheral blood flow have, like those with the other disease conditions already mentioned, a lowered oxygen concentration in mixed venous blood. This paper reports the results of studies of blood oxygen affinity from patients selected because of clinical and, in most cases, laboratory evidence of low cardiac output.

Methods

Patients were selected initially on the basis of clinical evidence of low cardiac output secondary to long-standing valvular heart disease. Patients with pulmonary or peripheral edema were excluded, as were smokers and patients whose blood oxygen capacities were lower than 17.0 ml/100 ml. Subsequently, in order to evaluate the data quantitatively, patients with clinical evidence of low cardiac output who were being subjected to cardiac catheterization were studied if the catheterization data showed an oxygen concentration difference between arterial and mixed venous blood greater than 5 ml/100 ml at rest.

For each study of blood oxygen affinity, venous blood was drawn without stasis into a syringe containing a solution of sodium fluoride and heparin. Equilibrium values of oxygen hemoglobin were determined using the "mixing technique" (12) at a carbon dioxide pressure (P<sub>CO<sub>2</sub></sub>) of approximately 40 mm Hg and at 37°C. At least two values of blood oxygen pressure (P<sub>O2</sub>) and pH, one between 40% and 50% saturation and the other between 50% and 60% saturation with oxygen, were determined in each study. The observed values of P<sub>O2</sub> were corrected to a standard plasma pH of 7.40 (13) and plotted on linear coordinates at saturation values calculated for each mixture by correcting for dissolved oxygen.
TABLE I
Cardiac output, Arteriovenous Oxygen Concentration Differences, and Blood Oxygen Capacities of Patients with Low-Output Heart Failure with Calculated Values for $P_{50}$

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cardiac output (L/min/m²)</th>
<th>$C_{O_2}$</th>
<th>$C_{O_2}$</th>
<th>Oxygen capacity (ml/100 ml)</th>
<th>$P_{50}$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. A.</td>
<td>1.4</td>
<td>10.5</td>
<td>17.1</td>
<td>32.0</td>
<td></td>
</tr>
<tr>
<td>B. J.</td>
<td>2.3</td>
<td>7.8</td>
<td>19.0</td>
<td>29.6</td>
<td></td>
</tr>
<tr>
<td>B. L.</td>
<td>2.4</td>
<td>6.2</td>
<td>19.2</td>
<td>29.0</td>
<td></td>
</tr>
<tr>
<td>E. E.</td>
<td>2.2</td>
<td>6.1</td>
<td>18.5</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>L. E.</td>
<td>3.5</td>
<td>5.8</td>
<td>21.3</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td>E. W.</td>
<td>2.0</td>
<td>6.8</td>
<td>19.2</td>
<td>26.8</td>
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</tr>
<tr>
<td>A. J.</td>
<td>2.3</td>
<td>6.7</td>
<td>17.5</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>F. E.</td>
<td>1.9</td>
<td>7.5</td>
<td>18.5</td>
<td>30.0</td>
<td></td>
</tr>
<tr>
<td>D. G.</td>
<td>2.8</td>
<td>5.4</td>
<td>17.9</td>
<td>31.8</td>
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<tr>
<td>L. C.</td>
<td>2.2</td>
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<td>S. L.</td>
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<tr>
<td>S. D.</td>
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<td>6.9</td>
<td>10.1</td>
<td>29.4</td>
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</tr>
</tbody>
</table>

**MEAN**

- Cardiac output: 2.2
- $C_{O_2}$: 6.9
- $C_{O_2}$: 10.1
- Oxygen capacity: 1.8
- $P_{50}$: 1.9

For details see text.

Discussion

The availability of oxygen to its sites of utilization in tissue cells depends upon the constancy of the external environment and also upon an integrated series of supply mechanisms which include ventilation, diffusion across the alveolocapillary membrane, transport from lungs to tissue capillaries, and diffusion from capillary blood to intracellular enzyme chains. The last of these processes is, according to evidence currently available, a passive (physical) process whose rate depends upon several physiological variables including the mean diffusion distance, the surface area for diffusion, and the gradient of oxygen tension between capillary blood and tissue cells. Present evidence (15) suggests that the level of intracellular oxygen is at most only a few millimeters of mercury, so the gradient for oxygen delivery depends largely upon the oxygen tension in capillary blood. That tension is, in turn, regulated (at a fixed rate of tissue oxygen consumption) by the rate of hemoglobin flow (the rate of blood flow multiplied by the oxygen-carrying capacity of
Changes in the oxygen affinity of blood (expressed at standard values of plasma pH and temperature) occur in humans when tissue oxygen supply is handicapped by residence at high altitude or by any of several diseases. The data presented here show that this adaptation is employed by patients whose tissue oxygen supply is compromised by low rates of blood flow secondary to heart disease. The utility of the observed change in maintaining the oxygen tension of blood in the average capillary is illustrated by Figure 1. The patients we studied extracted, on the average, 38% of the oxygen from their arterial blood during transit through peripheral tissues. This extraction contrasts with one of 21% in normal individuals (11). Because of the rightward displacement of the blood oxygen dissociation curve, the increased extraction would lower the oxygen tension in mixed venous blood from the value of 40 mm Hg which is found in normal resting humans (11).
to approximately 33 mm Hg. If their blood had retained a normal affinity for oxygen, the mixed venous oxygen tension would have fallen to 30 mm Hg with an oxygen extraction of 38%. Displacement of the blood oxygen dissociation curve, by itself, prevents about 30% of the fall in venous blood oxygen tension that would occur in patients with this degree of limitation of cardiac output if their blood oxygen affinity did not change. It is important to note that other mechanisms, such as changes in hydrogen ion concentration, also influence oxygen affinity. For instance, metabolic acidosis would displace the curve still further to the right, acting additively to the change reported here to support oxygen tension in tissue capillaries.

We regard lowered oxygen affinity of blood as an adaptive mechanism available to the human organism when its tissues are threatened with hypoxia. A 33% increase in cardiac output would elevate mixed venous oxygen tension to 33 mm Hg without the observed change in oxygen affinity, but seems to be an unavailable or, at least, less acceptable alternative for patients with low output heart failure.

A possible mechanism for changes in oxygen affinity found in blood from patients threatened with tissue hypoxia is suggested by the work of Benesch and Benesch (17), showing that deoxygenated hemoglobin removes 2, 3-diphosphoglycerate from its free state in the red cell and stimulates glycolysis to replenish the erythrocyte's stores of it and other organic phosphates. 2, 3-Diphosphoglycerate has been shown to decrease hemoglobin's affinity for oxygen (18, 19), and on the basis of these findings, we have previously postulated (10) that changes in its concentration within the red cell seem at present to offer the most attractive hypothesis for the changes observed in these patients with low cardiac output, other modifications in the environment of hemoglobin, such as increased acidity (20, 21), cannot be discarded as possibilities.

A vital function of the circulation is to maintain an oxygen tension in peripheral capillary blood adequate to supply oxygen to intracellular sites of utilization. Capillary oxygen tension depends upon the rate of oxygen flow with respect to oxygen consumption and upon the respiratory characteristics of circulating blood including oxygen affinity. In considering the therapeutic management of a patient with restricted cardiac output, the oxygen affinity of blood should be regarded as subject to regulation. For example, blood stored under usual conditions shows a definite increase in oxygen affinity within a few days (22) and the high affinity persists at detectable levels for several hours after transfusion (5). Such blood, when used in the treatment of shock, is predictably less effective in delivering oxygen to tissues than blood with normal or decreased oxygen affinity would be. Similarly, exposure to carbon monoxide at levels experienced by smokers causes both an increase in blood oxygen affinity and a decrease in the concentration of functional hemoglobin (23). For both reasons, smoking jeopardizes tissue oxygen supply. Procedures for maintaining tissue oxygenation should take into account factors that influence blood's oxygen affinity as well as those that maintain blood's oxygen capacity.

References

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