Importance of oxygen-haemoglobin binding to oxygen transport in congestive heart failure

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Abstract

Objective—To assess the importance of 2,3-diphosphoglycerate (2,3-DPG) and oxygen-haemoglobin binding to oxygen transport in patients with congestive heart failure.

Methods—In 30 patients with severe congestive heart failure, arterial, mixed venous, and coronary sinus venous blood concentrations of 2,3-DPG were measured and systemic output and coronary sinus blood flow were measured by a thermodilution technique. Oxygen-haemoglobin affinity was expressed as the oxygen tension in mm Hg at which blood is 50% saturated with oxygen (P50). Significant gradients between arterial, mixed venous, and coronary sinus blood 2,3-DPG concentrations were also found (mixed venous = 2.40 μmol/ml, p = 0.05 v arterial blood; coronary sinus venous blood = 2.23 μmol/ml, p < 0.04 v arterial blood). P50 was correspondingly high compared with the accepted normal value (mean 29.7 mm Hg, normal 26.6 mm Hg, p < 0.001). Systemic oxygen transport (351 ml/min/m2) varied directly with the forward cardiac index (r = 0.69, p < 0.0001). There was no relation between systemic oxygen transport and arterial oxygen content. Similarly, myocardial oxygen transport was found to vary directly with coronary sinus blood flow. Calculations of changes in cardiac index and coronary sinus blood flow at normal oxygen-haemoglobin binding indicate that a considerable increase in cardiac index and coronary blood flow would be required to maintain similar systemic and myocardial oxygen transport.

Conclusions—In patients with severe heart failure increased 2,3-DPG and reduced oxygen-haemoglobin binding may be compensatory mechanisms that maintain adequate systemic and delivery of oxygen to myocardial tissue.

Patients and methods

Thirty patients with congestive heart failure and New York Heart Association (NYHA) class III or IV were studied. The underlying cause of congestive heart failure was coronary artery disease in 27 and idiopathic dilated cardiomyopathy in three. All patients had left ventricular ejection fractions of 40% or less. They were all studied as inpatients at the Moffitt Hospital, University of California, San Francisco, for the management of congestive heart failure. This study was approved by the Institutional Review Board and all patients gave informed consent. Pulmonary artery and coronary sinus catheters were placed by standard percutaneous techniques and their positions were confirmed by fluoroscopy. Cardiac indices (l/min/m2) were measured by a thermodilution technique.  

Systemic oxygen transport (the quantity of oxygen delivered to tissues for aerobic respiration) may be impaired due to reductions of either cardiac output, oxygen content of arterial blood, or the haemoglobin content of blood. In congestive heart failure, forward cardiac output may be reduced, decreasing the quantity of oxygenated blood carried to the periphery. The oxygen content of arterial blood and the haemoglobin concentration are nearly normal and are not the main factors limiting oxygen transport in patients with congestive heart failure.

Despite reductions in the cardiac output and systemic oxygen transport, systemic oxygen consumption is generally maintained by means of compensatory increases in tissue oxygen extraction. One of the mechanisms by which tissue oxygen extraction is enhanced is through a reduction in oxygen-haemoglobin affinity, favours the unloading of oxygen to tissues. The reduction in oxygen-haemoglobin affinity is accomplished through increased synthesis of 2,3-diphosphoglycerate (2,3-DPG) in erythrocytes. The organic phosphate 2,3-DPG is high in patients with lung disease, cyanotic congenital heart disease, and low output congestive heart failure. Little information is available, however, about the potential importance of the 2,3-DPG concentrations in erythrocytes to the enhancement of tissue oxygen extraction in these clinical circumstances. In this report, we present data on 2,3-DPG concentrations and oxygen-haemoglobin binding in 30 patients with severe congestive heart failure due to impaired left ventricular systolic function. We also evaluate the contribution of a reduced oxygen-haemoglobin affinity to systemic and myocardial oxygen transport and its use in these patients.
with the patient supine and fasting. A minimum of three measurements were made for each patient and these were averaged. Coronary blood flow (ml/min) was estimated by a continuous thermodilution technique\(^1\) with Wilton-Webster coronary sinus catheters (Altadena, California), and infusion of 5% dextrose in water at room temperature at a rate of 46 ml/min. Oxygen saturations of arterial, pulmonary arterial (mixed venous), and coronary sinus blood were measured directly with a haemoximeter (Radiometer, model OSM-2, Copenhagen, Denmark). Haemoglobin content was measured by the cyanmethaemoglobin method. Blood gases were measured in arterial, mixed venous, and coronary sinus blood with an automated blood gas analyser (Corning Medical, model 168 and 178, Medfield, Massachusetts). Oxygen contents were then calculated directly from the measured data with the formula: 
\[ \text{oxygen content (vol %)} = \text{oxygen saturation/100 x haemoglobin content (g %)} \times 1.34 (ml/g) + 0.0031 \text{ PaO}_2 \text{ mm Hg}. \]

The other indices were calculated as follows: systemic oxygen transport (ml O\(_2\)/min/m\(^2\)) = (arterial O\(_2\) content x cardiac index x 10); myocardial oxygen transport (ml O\(_2\)/min) = (arterial O\(_2\) content x coronary blood flow)/100; systemic oxygen consumption (ml O\(_2\)/min/m\(^2\)) = tissue oxygen extraction x cardiac index x 10; myocardial oxygen consumption = coronary blood flow/100 x (arterial O\(_2\) content - coronary sinus O\(_2\) content).

Oxygen-haemoglobin affinity is expressed as the oxygen tension (mm Hg) at which blood is 50% saturated with oxygen (P\(_{50}\)). The P\(_{50}\) of blood was calculated for each patient from directly measured oxygen saturations and oxygen tensions of mixed venous blood measured by the method of Severinghaus.\(^2\) Measured oxygen tensions were corrected to pH 7.40 before the calculation of P\(_{50}\). Whole blood concentrations of 2,3-DPG were measured in triplicate on arterial, mixed venous, and coronary sinus blood samples deproteinised in 0.5 M cold perchloric acid with an NAD/NADH spectrophotometric assay (Sigma Chemicals, St. Louis, Missouri).\(^2\)

The contribution of reduced oxygen-haemoglobin binding to oxygen transport was assessed as follows. The directly measured oxygen tensions and pH values for each blood sample on each individual patient were applied to the normal oxygen-haemoglobin binding curve to determine normalised oxygen saturations (P\(_{50}\) = 26.6 mm Hg). Normalised oxygen contents were then determined from normalised oxygen saturations. Normalised oxygen contents were used to recalculate values for coronary blood flow and cardiac index assuming constant oxygen consumption (systemic and myocardial oxygen transport and oxygen consumption). Comparison of the calculated values for coronary blood flow and cardiac index with measured values gives a quantitative estimate of the amount that coronary blood flow and cardiac output would need to increase to maintain constant concentrations of oxygen delivery and consumption if oxygen-haemoglobin binding were normal.

Statistical analyses were performed on P\(_{50}\) data with unpaired t tests. Normal values for P\(_{50}\) (26.6 mm Hg) were taken from the publication of Severinghaus in which 10 healthy non-smoking volunteers were studied.\(^2\) Data on 2,3-DPG concentrations were compared with the normal population by single group t tests and the population mean value was 2.1 nmol/ml in whole blood.\(^2\) Statistical comparisons were made of 2,3-DPG data between arterial, mixed venous and coronary sinus blood samples with paired t tests. Differences between groups were considered significant when p < 0.05. All statistical analyses were performed with a Macintosh computer and a Statview statistical software package (version 1.1, Calabasass, California), and the data are presented as means (SEM) unless otherwise indicated.

**Results**

2,3-DIPHOSPHOGLYcerate

The mean (SEM) arterial concentration of 2,3-DPG in patients with heart failure was 2.58 (0.18) μmol/ml in whole blood, or 20.8 (1.4) μmol/g haemoglobin, which is higher than reported normal values. A gradient between arterial, mixed venous, and coronary sinus 2,3-DPG concentrations was also found (fig 1). Mixed venous 2,3-DPG concentrations were significantly lower (2.40 (0.17) μmol/ml p = 0.05) than arterial concentrations and coronary sinus 2,3-DPG concentrations were the lowest (2.23 (0.22) μmol/ml, p = 0.038). The arterial venous gradient for 2,3-DPG might be explained by a larger than normal gradient for hydrogen ions and carbon dioxide. The blood pH was 0.07 units lower in coronary sinus blood than in arterial blood, and the carbon dioxide tension was 14.2 mm Hg greater (table 1). The mixed venous pH was on average 0.05 units lower and the carbon dioxide tension 8.7 higher than arterial blood, indicating arterial to venous hydrogen ion and carbon dioxide gradients about 50% greater than normal.

![Figure 1: Simultaneous measurements of 2,3-DPG in arterial, mixed venous, and coronary sinus blood. Note the progressive gradient between arterial, mixed venous, and coronary sinus 2,3-DPG concentrations.](image)
Table 1 Blood gases

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Mixed venous</th>
<th>Coronary sinus</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.454 (0.001)</td>
<td>7.404 (0.001)</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>34.2 (1.1)</td>
<td>42.9 (0.9)</td>
</tr>
<tr>
<td>Pac (mm Hg)</td>
<td>98.7 (6.9)</td>
<td>31.7 (1.4)</td>
</tr>
<tr>
<td>HCO3 (meq/l)</td>
<td>23.7 (6.7)</td>
<td>26.7 (0.6)</td>
</tr>
</tbody>
</table>

Values are means (SEM). Paco2, carbon dioxide tension; Pac, oxygen tension; HCO3, bicarbonate anion.

OXYGEN-HAEMOGLOBIN BINDING

Corresponding measures of oxygen-haemoglobin binding (P50) were high in all but one of the 30 patients studied (fig 2). The mean P50 was 29.7 (0.4) mm Hg v 26.6 mm Hg normally (p < 0.001). There were no correlations between 2,3-DPG concentrations and the measured P50.

SYSTEMIC OXYGEN TRANSPORT AND CONSUMPTION

Systemic oxygen transport was 351 (16) ml O2 min⁻¹, and was related to cardiac index (2.2-31 (0.15) l/min m²). Arterial haemoglobin content was 12.5 (0.04) g/dl and oxygen content was 16.0 (0.5) vol%. A significant linear relation between systemic oxygen transport and cardiac index was found as expected (r = 0.89, p < 0.001) (fig 3). There were no correlations between systemic oxygen transport and arterial oxygen content (fig 3).

MYOCARDIAL OXYGEN TRANSPORT AND CONSUMPTION

Myocardial oxygen transport was 21.8 (2.9) ml O2/min and consumption was 16.7 (2.2) ml O2/min. As expected, myocardial oxygen transport was dependent on coronary blood flow (r = 0.97, p < 0.0001) (fig 4). Myocardial oxygen consumption was also related to coronary blood flow (r = 0.96, p < 0.0001), but not myocardial oxygen extraction (fig 4).

CONTRIBUTION OF REDUCED OXYGEN-HAEMOGLOBIN BINDING TO OXYGEN TRANSPORT

Normalisation of oxygen-haemoglobin binding would result in a 6.2% rise in the mixed venous oxygen saturation (p < 0.001) and a 7.4 mm Hg rise in the coronary sinus oxygen saturation (p < 0.001) assuming no change in arterial oxygen saturation. Corresponding mixed venous oxygen content would rise 1.1 vol% (p < 0.001) and coronary sinus oxygen content 1.2 vol% (p < 0.001). Systemic and myocardial oxygen extraction rates would therefore fall about 1.2 vol% each (table 2). To compensate for this, the resting cardiac index would need to be 31% higher to maintain the same systemic oxygen delivery. Similarly, coronary blood flow would need to be considerably higher to maintain the same myocardial oxygen delivery and consumption (table 2).

Figure 2 Plot of measured mixed venous oxygen tensions and saturations in the 30 patients compared with the normal adult oxygen-haemoglobin binding curve.

Figure 3 Relation between forward cardiac index and systemic oxygen transport. Note that the arterial oxygen content bears no relation to overall systemic oxygen transport.

Figure 4 Relation between coronary blood flow and myocardial oxygen transport. There was no relation between arterial oxygen content and overall oxygen transport to the myocardium; myocardial oxygen transport was related to coronary blood flow, as expected.
Table 2  Effect of normalisation of oxygen-haemoglobin binding

<table>
<thead>
<tr>
<th></th>
<th>Reduced O2 binding</th>
<th>Normalised O2 binding</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P0 (mm Hg)</td>
<td>29-7 (0-4)</td>
<td>26-6 (0-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed venous O2 saturation (%)</td>
<td>52 (0-2)</td>
<td>50-2 (2-6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary sinus O2 saturation (%)</td>
<td>23-8 (1-5)</td>
<td>31 (2-17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed venous O2 content (vol %)</td>
<td>8-8 (0-6)</td>
<td>9-8 (0-6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary sinus O2 content (vol %)</td>
<td>3-9 (0-3)</td>
<td>5-1 (0-3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue oxygen extraction (vol %)</td>
<td>7-2 (0-5)</td>
<td>6-1 (0-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial oxygen extraction (vol %)</td>
<td>11-7 (0-5)</td>
<td>10-5 (0-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m2)</td>
<td>2-31 (1-5)</td>
<td>2-94 (0-34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min)</td>
<td>142 (12)</td>
<td>209 (28)</td>
<td>0-006</td>
</tr>
</tbody>
</table>

Values are means (SEM).

Discussion

Decreased oxygen-haemoglobin binding is known to be an important adaptive mechanism in clinical circumstances where oxygen transport is inadequate, including patients with anaemia, chronic hypoxia due to intrinsic lung disease, high altitude, or cyanotic congenital heart disease, and in patients with low output congestive heart failure. The factors directly affecting oxygen-haemoglobin binding include the blood hydrogen ion and carbon dioxide concentrations, and erythrocyte concentrations of 2,3-DPG. An increase in 2,3-DPG concentrations is an important adaptive mechanism by which oxygen-haemoglobin binding is reduced. In this study of patients with severe congestive heart failure oxygen-haemoglobin binding was substantially reduced and 2,3-DPG concentrations were higher than normal published values. The results of our study suggest that the reduced oxygen-haemoglobin binding may be an important adaptive mechanism to maintain adequate oxygen transport in congestive heart failure. In our patients elimination of this adaptive mechanism would necessitate an increase in cardiac output of 31% and coronary blood flow of 57% to meet the same resting metabolic demands. In the presence of limited cardiac and coronary reserve, a lack of reduction in oxygen-haemoglobin binding could potentially aggravate the imbalance of metabolic demands and tissue oxygen supply often present in patients with heart failure. In another study, we found that normalisation of oxygen-haemoglobin binding by induction of acute metabolic alkalosis in similar patients resulted in substantial reductions of systemic and myocardial oxygen, which often lead to myocardial ischaemia. Thus reduced oxygen-haemoglobin binding seems to play a part in maintaining oxygen delivery to the tissues, particularly to the myocardium, in patients with severe congestive heart failure.

Another finding of interest in our study was the gradient for 2,3-DPG between arterial, mixed venous, and coronary sinus blood. The precise explanation for the arterial venous gradient for 2,3-DPG remains unclear. In a previous study, we also found a higher coronary sinus P0 compared with that of mixed venous blood. This phenomenon may be partly explained by phasic alterations in acid base balance. Our patients with congestive heart failure have greater differences than normal in hydrogen ion and carbon dioxide concentrations between arterial, mixed venous, and coronary sinus blood (table 1). Synthesis of 2,3-DPG falls in acidic blood and rises in alkaline blood. This is due to slower rates of glycolysis within erythrocytes at lower pH values, making less substrate available for 2,3-DPG synthesis in acidic blood. Also, metabolism of 2,3-DPG is faster at lower pH values: the enzyme responsible for the degradation of 2,3-DPG has an optimum pH of 7.20. Greater than normal differences in blood pH between arterial, mixed venous, and coronary sinus blood may thus result in greater than normal differences in both synthesis and metabolism of 2,3-DPG. The present findings also indicate that the effects of blood pH on 2,3-DPG synthesis occur rapidly as blood passes through the capillary beds.

The differences in 2,3-DPG concentrations in venous and arterial blood may have physiological relevance. Lower venous concentrations may facilitate oxygen uptake in the lungs and higher arterial concentrations may facilitate unloading of oxygen to the tissues. Differences in acid base balance between arterial and venous blood are more pronounced in circulatory shock and cardiopulmonary arrest and in such clinical circumstances, these potential adaptive mechanisms may be more relevant.

These presumed compensatory changes in oxygen-haemoglobin binding are likely to be more important in the light of the fact that both systemic and myocardial oxygen transport are primarily dependent on cardiac output and coronary blood flow, as was found previously in patients with congenital heart disease and in normal human volunteers. As a result, shifts of oxygen-haemoglobin binding toward normal in these patients would necessitate commensurate increases in cardiac output and coronary blood flow to maintain the balance between a tissue oxygen supply and demand.

Experimental studies suggest that agents that directly reduce oxygen-haemoglobin binding, such as o-iodosobenzonate, dihydroxy acetone phosphate, and pyruvate may decrease the extent of myocardial injury by 30%-40% during acute coronary occlusion. The effects of these agents in patients with congestive heart failure have not been evaluated. Erythropoietin increases the 2,3-DPG content of erythrocytes but has not been tested in patients with congestive heart failure. Nevertheless, the results of our study suggest that such agents might be of benefit in the treatment of congestive heart failure and deserve further investigation.

There are several limitations of this study. We did not determine the values of 2,3-DPG and P0 in normal people concurrently but used the values that are widely accepted as normal. A significant variability in the 2,3-DPG concentrations and of P0 in patients with chronic hypoxic lung disease has been found.

In our previous study on patients with normal left ventricular systolic function and...
without heart failure, calculated P50 concentrations were 26±1 (2-0) mm Hg. Furthermore, we found close agreement between the one point technique and the method of direct measurement of P50. With methods similar to ours, several studies have shown SDs of about 1 mm Hg in P50 measurements. In the present study, the SD of P50 values was similar. It is thus unlikely that this inadequacy would have influenced the results qualitatively. We also did not measure systemic and coronary haemodynamics concurrently in a control group. In a previous study, however, we determined systemic and coronary haemodynamics concurrently in patients with heart failure.

In these patients the cardiac index was 3·0 (0·6) l/min/m². Coronary blood flow was 74±0 (37) l/min and myocardial oxygen consumption was 3·7 (4·2) mmol/min. Thus in patients with heart failure in this study, both coronary blood flow and myocardial oxygen consumption were considerably higher, and cardiac index lower than normal. The other limitation is that change in these adaptive mechanisms were not assessed during stress. Nevertheless, the results suggest that even in the resting condition a number of compensatory mechanisms are called upon to maintain adequate delivery of oxygen to the tissues of patients in severe heart failure, and decreased oxygen-haemoglobin binding associated with increased 2,3-DPG is probably one of them.

The study was supported by grants from the National Heart, Lung, and Blood Institute (No HL-01791) and the American Heart Association (No 88-1185).

RMB was a recipient of the Physician-Scientist Award of the National Institute of Health, and is a Winthrop Pharmaceutical Grant-in-Aid Awardee of the American Heart Association. CW was a recipient of the Clinical Investigator Award of the National Institutes of Health. KC is the Lucien Stern Professor of Cardiology of the University of California, San Francisco.