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Ischemia may be less detrimental than anemia for O_2 transport because of CO_2 transport: a model analysis

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Abstract: We analyzed the relationship between oxygen delivery (Do_2) and Pto_2 (tissue Po_2). We found an important factor which has not been specified before. In the previous O_2 transport model, Do_2 was a dependent variable, calculated from hemoglobin, blood flow, Pao_2, and the oxygen dissociation curve (ODC). In this study, the model was modified slightly so that the Do_2 can be an independent variable. We allowed, instead, one of the three parameters, hemoglobin, blood flow, and Pao_2 to be a dependent variable. We compared the brain tissue Po_2 under three conditions, hypoxemia, ischemia and anemia, at the same Do_2. To further elucidate the mechanism produced by the effect of CO_2 transport on the ODC, we studied the effect of the Bohr factor (d log Po_2/d pH) and of the gas exchange ratio (Vco_2/Vo_2) on the O_2 transport. Ischemia maintains a slightly higher tissue Po_2 than anemia at the same Do_2 level. In ischemia the CO_2 transport is disturbed, leading a higher draining venous Pco_2, which in turn maintains a higher Po_2 at the capillary, resulting in a higher gradient for Po_2 between capillary and the tissue. Between ischemia and anemia, ischemia is less detrimental than anemia. In ischemia, the CO_2 transport is disturbed, which in turn maintains a higher Po_2 at the capillary.

Key words: Oxygen transport, Low blood flow, Hemoglobin, Oxygen dissociation curve, CO_2 exchange

Introduction

Among various parameters, Do_2 (O_2 delivery: Cao_2 x blood flow) affects the tissue oxygenation most. Do_2 is composed of three parameters: Pao_2, blood flow, and hemoglobin. Causes of decreased Do_2, therefore, are classified usually into three categories: hypoxemia (low Pao_2), ischemia, and anemia. Compared at the same Do_2, hypoxemia is most detrimental. It should be so theoretically, and has been proven experimentally. In hypoxemia, the pressure gradient to move oxygen from the capillary to the tissue is markedly reduced, resulting in tissue hypoxia. Between ischemia and anemia, the difference is not very clear, but the experiment shows that, if there is a difference, anemia is probably more detrimental than ischemia when compared at the same Do_2.

We attempted to approach this question of the relationship between the mode of decreased Do_2 and Pto_2 using a previously developed O_2 transport model. We found an important factor which has not been specified before. Between ischemia and anemia, there is a marked difference in CO_2 transport, which in turn affects the oxygen dissociation curve (ODC) through the Bohr shift.

Methods

In the original O_2 transport model, which had been developed and analyzed previously, Pao_2, hemoglobin, and blood flow were all treated as independent variables. Do_2 was calculated from these values when necessary. Pto_2 (tissue Po_2) was then calculated accordingly [1,2]. This original model was inconvenient to compare Pto_2 at a defined Do_2.

The model, therefore, was modified so that the Do_2 can be defined as an independent variable. In this model, we first define the Do_2. The calculation was then divided into three routes. For each condition, the other two parameters were held constant to normal values. For ischemia, for example, the Do_2 was decreased by reducing blood flow, while Pao_2 and hemoglobin remained normal.

This mode requires somewhat complex iterative calcuation. The 2,3DPG, the arterial pH, and the $Paco_2$ were maintained normal. The organ studied was the

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brain, taken as a whole. Therefore, the blood flow corresponds to the cerebral blood flow (CBF). We compared the Pto_2 at the same Do_2. Unless specified otherwise, the gas exchange ratio of that tissue was assumed to be unity.

To further elucidate the mechanism, we studied the effect of the Bohr factor (d log Po_2/d pH) of the ODC on the O_2 transport. We also studied the effect of the gas exchange ratio of the tissue (RQ: respiratory quotient: Vco_2/Vo_2). The Do_2 were varied from 10 ml/100 g/min (normal value) to zero in 0.2 decrements. The Bohr factors were varied in four levels: zero, −0.24, −0.48 (normal), and −0.72. RGs were varied in three levels: 1 (normal), 2, and 3. Other conditions are described elsewhere.

Results

Among the three conditions of hypoxemia, ischemia, and anemia, hypoxemia resulted in the lowest Pto_2 throughout the entire range of Do_2 studied (Fig. 1). The difference is quite marked. Between ischemia and anemia at the same Do_2, ischemia maintained a slightly higher Pto_2 than anemia. Numerical values of Pto_2 and $Pjvo_2$ (jugular venous Po_2) under three conditions are given in Table 1 for Do_2 of normal, half normal, and one-third of normal.

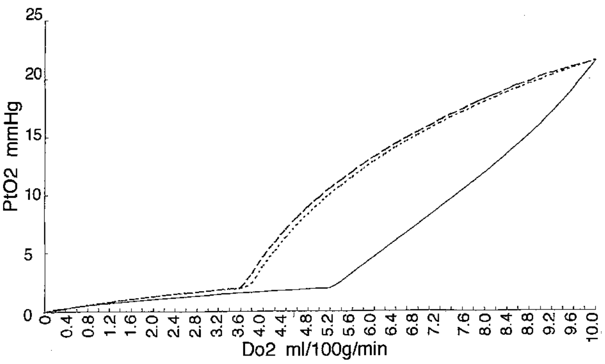

Fig. 1. The relationship between Do_2 and Pto_2 when Do_2 decreases in three conditions: hypoxemia (*solid line*) decreased Pao_2, ischemia (dashed line), or anemia (dotted line) Do_2 of 10 ml/100 g/min is the normal value used in this model. At the same Do_2, hyposemia results in markedly lower Pto_2 than the other two conditions. The Pto_2 is slightly lower in anemia than in ischemia for most of the Do_2

Tahle 1. Pto_2 and $Pjvo_2$ (mmHg) at three levels of Do_2 (ml/100 g/min)

Do_2	10 (norm)		5 (1/2 norm)		3.33 (1/3 norm)	
	Pto_2	$Pjvo_2$	Pto_2	$Pjvo_2$	Pto_2	$Pjvo_2$
Hypoxemia	21.0	34.6	1.93	16.4	1.45	12.3
Ischemia	same		9.68	21.9	1.86	15.4
Anemia	same		9.14	22.5	1.83	14.9

Pto_2 and $Pjvo_2$ values for Do_2 of 10 ml/100 g/min are those for normal Pao_2 CBF, and hemoglobin.

The increase in the value of the Bohr effect improved the Pto_2 at the same Do_2 over almost the entire range studied (Fig. 2). The improvement is more marked in the range of moderate reduction of Do_2. Increase in the RQ value also improved markedly the Pto_2 at the same

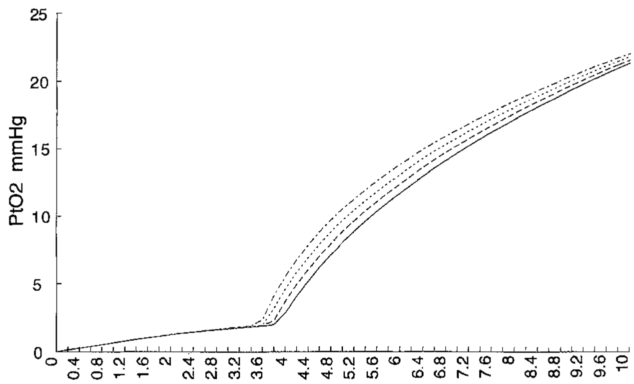

Fig. 2. The relationship between Do_2 and Pto_2 when the Bohr factor of the blood was varied between 0 and −0.72, its normal value being −0.48. Data shown are for those in ischemia. The effects are somewhat less in anemia. It should be noted that the effect of the Bohr factor becomes smaller as Do_2 approaches the normal value of 10. When the transport capacity is plentiful, its quality becomes relatively unimportant. *solid line*, BF = O; *dashed line*, BF = −0.24; *dotted line*, BF = −0.48; *chained line*, BF = −0.72

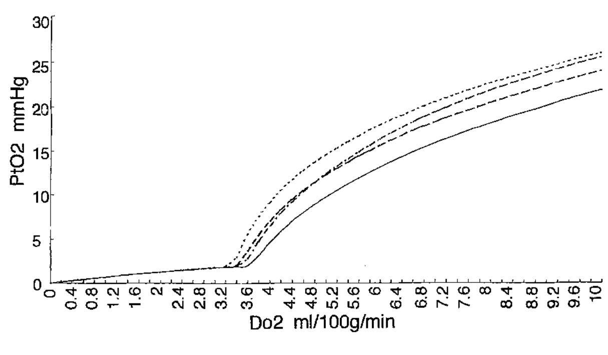

Fig. 3. The relationship between Do_2 and Pto_2 when the RQ value was varied between 1 and 3, its normal value being 1. Three lines for *ISC* are for those in ischemia. The line for *ANE* is for that in anemia. The line for RQ = 1 with Do_2 decreased by anemia is not shown here, but is shown in Figure 1. This figure makes three points. An increase in RQ, or an increase in CO_2 transport relative to oxygen transport, improves the oxygen transport itself. This effect is more marked for ischemia than for anemia. The difference between ischemia and anemia iis more marked in the moderate reduction of Do_2. *Solid line*, RQ = 1:ISC; *dashed line*, RQ = 2:ISC; *dotted line*, RQ = 3:ISC; *Chained line*, RQ = 3:ANE; ISC, ischemia; ANE anemia

Do_2 (Fig. 3). Improvement was observed both in ischemia and in anemia, but it was more in ischemia.

Discussion

At the same Do_2 levels, hypoxemia is considered theoretically and shown experimentally to be far more detrimental than ischemia and anemia [3]. In the range of interest of decreased Do_2, the Pao_2 decreases markedly and the Po_2 gradient from the capillary to the tissue decreases as well.

This decreased Po_2 gradient from the capillary to the tissue affects the oxygen transport markedly. For the oxygen to be transported effectively, not only the amount of oxygen but the pressure gradient is required, and hypoxemia tends to fail to supply this pressure gradient even at a modestly decreased Do_2. For Do_2 of half normal, the pao_2 is less than 30 mmHG, which decreases markedly the pao_2 gradient from the capillary to the tissue.

Between the two other causes of decreased oxygen delivery, ischemia and anemia, the difference had not been that clear. Few experimental studies indicated that anemia may be more detrimental than ischemia at the same O_2 delivery. The difference was, however, relatively subtle and was not conclusive. Therefore, the mechanism underlying this difference, if ever it existed, had not been analyzed.

We originally thought that this difference was caused by the capillary network arrangement and flow characteristics of some nature. We therefore anticipated that similar findings cannot be demonstrated in such a simple O_2 transport model as we used. This model is quite straightforward. No capillary network structure or flow characteristics are incorporated.

The effects of CO_2 transport on O_2 transport have been analyzed by many researchers and re known to work beneficially during shock and during severe exercise [4]. Yet they have never been applied to the Do_2-Vo_2 relationship. In retrospect, this result could have been quite predictable. In ischemia, the CO_2 transport is disturbed because not only oxygen but the CO_2 has to be carried by the blood flow. This disturbed CO_2 exchange results in a higher tissue and draining venous Pco_2 values. These high Pco_2 values both at the tissue and at the capillary shift the ODC to the right and increase the Po_2 values at the capillary higher than otherwise. This creates a high gradient for Po_2 from the capillary to the tissue. In anemia, the CO_2 transport is not disturbed because CO_2 is carried not by hemoglobin but by plasma. Anemic blood carries CO_2 almost as well as nonanemic blood.

This mechanism was further confirmed by modifying the parameters of the blood: changing the Bohr factor and the RQ Value. The Bohr factor determines the degree of shift of the ODC by pH or Pco_2 change. If this factor is zero, the CO_2 loaded at the capillary causes no shift of the ODC. If the absolute value of this factor is large, then the VO_2 loaded at the capillary shifts the ODC markedly to the right. The capillary Po_2 is now higher, and this high capillary Po_2 improves the transport of oxygen to the tissue.

A larger RQ value means that the CO_2 load from the tissue to the capillary is greater. It then causes a larger shift of the ODC to the right, increases the capillary Po_2, and improves the oxygen transport. Increased RQ values may have more physiological and/or clinical relevance than simply elucidating the mechanism. It has been well established that in tissue hypoxia the apparent CO_2 production often increases markedly. Anaerobic metabolism is induced by tissue hypoxia and causes an increase in lactic acid and other acidic substance. The hydrogen ion thus produced, then, combines with the bicarbonate ions in the body fluid. The reaction is $H^+ + HCO_3^- \rightarrow H_2O + CO_2$. These CO_2 molecules are in addition to the regular CO_2 production and increase the Pco_2 of the tissue and the capillary [5–7]. Though quantitatively unknown, the value of RQ may well exceed the normal value of 0.8 at tissue in general and of 1.0 at the brain.

We took the brain tissue to analyze the relationship $Do_2 - Pto_2$. It should be noted, however, that similar analyses should apply and result in essentially the same findings in any tissue of the body. The differences between the brain and other organs are due to the relationship between the blood flow and the metabolism, including the RQ value. These affect the numerical values, yet they should not affect the underlying relationship and the conclusion.

Our findings do not rule out possibilities other than those we propose here. For example, if blood in anemia flows so fast through capillaries that hemoglobin does not have time to release oxygen, oxygen supply to the tissue may be disturbed more in anemia than in ischemia by this mechanism. Conversely, if we imagine that the capillary blood flow is more uneven in ischemia than in anemia, then oxygen supply to the tissue may be disturbed more in ischemia than in anemia. Such effects need to be studied in more elaborate experiments, and possibly in more detailed analytical models.

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