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Simulation of oxygen delivery to tissues: The role of the hemoglobin oxygen equilibrium curve at altitude

Michele Samaja,[1] Pietro E. diPrampero[2] and Paolo Cerretelli[2]
[1] *Dipartimento di Scienze e Tecnologie Biomediche, Universitá degli Studi di Milano, via Olgettina 60, 20132 Milano, Italy*
[2] *Département de Physiologie de l'Université, C.M.U., 1 rue Michel Servet, 1211 Genève 4, Switzerland*

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Summary

A simplified model is described to estimate the oxygen delivery to tissues as a function of oxygen uptake, gas exchange ratio, 2,3–DPG/Hb concentration ratio, arterial and venous PO_2, PCO_2 and pH. Due to the complexity of the oxygen delivery system, the aim of this model is to predict relative changes of the oxygen delivery to tissues induced by changes of the other variables, rather than to yield absolute values. In this work, the importance of the observed shifts of the hemoglobin oxygen equilibrium curve at altitude is evaluated in terms of the efficiency of the oxygen transport system. It will be shown that a rightward shift of the oxygen equilibrium curve is beneficial up to 5400 m.a.s.l., while for higher altitudes such shifts lead to less efficient oxygen delivery to tissues.

Introduction

The oxygen transport to tissues depends on many physiological and biochemical factors, each of which is intimately related to the others. It follows that the definition of a model that fully describes this system is a rather difficult task. The model reported here takes into account only some of the most important factors, i.e., oxygen uptake (VO_2), gas exchange ratio (R), hemoglobin (Hb) and intraerythrocytic 2,3-diphosphoglycerate (2,3-DPG) concentration, blood flow, arterial and venous PO_2, PCO_2 and pH. Other factors (such as tissues capillarization, pulmonary shunt, permeability of alveolar membrane to gases, blood viscosity, etc.) were not considered, and therefore the model does not allow exact quantitative predictions of oxygen transport. Nevertheless, we feel that the estimation of the relative changes of oxygen delivery to tissues as induced by changes of some or all the above factors is useful in several physiological and clinical studies.

A convenient way to represent the oxygen transport to tissues is a venous PO_2 vs. blood flow plot. Indeed, these two factors are the most difficult to be measured or assumed. Thus, the purpose of this program is to predict a venous PO_2 vs. blood flow relationship at constant selected values for the other parameters. Specifically, the aim of this work is to predict the changes of the oxygen transport induced by the shift of the Hb oxygen equilibrium curve (OEC) observed at moderate to extreme altitudes, that is mainly mediated by an increase of 2,3-DPG concentration and of pH. In fact, while

Address for offprints: Dr Michele Samaja, Dipartimento di Scienze e Tecnologie Biomediche, c/o Ospedale San Raffaele, via Olgettina 60, I-20132 Milano, Italy.

the effect of an increased pH and 2,3-DPG concentration on blood OEC is well known (Benesch and Benesch, 1967), it is still controversial whether the observed shifts of the OEC lead to positive or negative effects on the oxygen delivery to tissues. The simulated conditions will include both whole body oxygen transport and the oxygen transport in a single leg, using published data, both at rest and during exercise at different altitudes.

Description of the program

The program devised to simulate the oxygen delivery by blood is composed of the following brief routines.

ADAIR: calculates the 4 composite constants (Adair, 1925) which define an OEC from pH, pCO_2, and the 2,3-DPG/Hb molar concentration ratio (G) (Winslow et al., 1983).

FICK: computes blood flow from VO_2, [Hb], the oxygen solubility in blood, and partial pressures of arterial and venous gases, using the following equation:

$$Q = VO_2/\{[Hb]*0.0134*(S_aO_2 - S_vO_2) + aO_2*22.4*(P_aO_2 - P_vO_2)\}$$

where Q is blood flow (l/min), aO_2 is the oxygen solubility coefficient in blood from the routine OZALFA, SO_2 is the oxygen saturation, and notations 'a' and 'v' refer to arterial and venous, respectively.

HHCO2T: estimates total CO_2 content from pH and PCO_2 using the Henderson-Hasselbalch equation:

$$CO_2 \text{ content} = (aCO_2*PCO_2)*[1 + 10^{(pH-pK)}]$$

where the value for aCO_2 (solubility coefficient of CO_2 in blood) is 0.0306 at 37° C (Severinghaus, 1971), and pK is calculated as:

$$pK = 6.099 - 0.04167*(pH - 7.4)$$

(Severinghaus, 1971).

HHPH: same as HHCO2T, but calculates pH from total CO_2 content and PCO_2.

INPUT: reads sequentially from an external device (for example, a disk file) the following values: the name of the output file containing computed values, VO_2 (l/min), [Hb] (g/dl), G, the gas exchange ratio (R), higher and lower venous PO_2 bounds (torr), and arterial blood Base Excess (MEq/l), PO_2 (torr), and PCO_2 (torr). The file containing these data was prepared using a text editor or a separate subprogram.

OPENF: opens the output file(s) with the same name as read from INPUT.

OUTPUT: outputs computed data (venous PO_2, PCO_2, pH, oxygen saturation, Base Excess, total CO_2 content, and blood flow).

OZALFA: computes the oxygen solubility (mM/torr) in blood from temperature (Roughton and Severinghaus, 1973).

PHI: computes intracellular pH (pH_i) from plasma pH and G, using the following equations:

$$A = 0.0077 + 0.11*G$$
$$B = 0.071 + 0.098*G$$
$$C = -0.0036 + 0.087*G$$
$$pH_i = pH - A - B*P - C*P*P$$

where $P = (pH - 7)$. These equations are derived from a previously described nomogram (Samaja and Winslow, 1979).

SAT: calculates the oxygen saturation from the 4 Adair constants and PO_2 (Adair, 1925).

Thomas: computes Base Excess from pH, PCO_2, hematocrit, concentration of plasma proteins, oxygen saturation, pH_i, as from an algorithm described by Thomas (1972).

The purpose of the main program is to define the relationship between venous PO_2 and the blood flow necessary to supply the required amount of oxygen at constant values for the other variables.

This can be accomplished as follows.

First, arterial blood pH, oxygen saturation, and CO_2 content are calculated from the data entered through the INPUT routine, including plasma protein concentration and temperature, the values of which are routinely set to 70 g/l and 37° C, respectively. Venous blood parameters can be estimated, for a given venous PO_2 range (1 torr steps), by successive iterations of the values for venous pH and PCO_2. Briefly, from the given pH/PCO_2 values, the venous OEC is computed, and hence the blood flow necessary to transport the required amount of oxygen at the current venous PO_2 value. From these values, the venous Base Excess is calculated and compared to the arterial one. A blood flow value is also calculated from a mass balance relationship for CO_2, using the HHCO2T routine described above and the gas exchange ratio. When the venous and arterial Base Excess values coincide within 0.1 mEq/l, and when the two calculated blood flows match each other, the current set of values (pH, PCO_2, blood flow, etc.) is accepted, and the program exits and begins, if necessary, another loop at another venous PO_2 value.

Results

The FORTRAN program runs on a Digital Professional 350 personal computer. The size of the core pool memory required in a standard version is less than 24,000 words. Execution time is less than 30 sec for each simulation.

Depending on the values input to the program, several conditions can be studied. In the present work, we have analyzed the relationship between venous PO_2 and blood flow during maximal aerobic exercise at increasing altitude from sea level to 8848 m, for the whole body and a single leg. Table 1 shows the values used for the simulations together with their sources, the only exception being R, for which the value of 1.0 was assumed throughout. The value of VO_2 for a single leg was inferred from the work of Jorfeldt and Wahren, 1971.

Figures 1 and 2 show the resulting venous PO_2 vs. blood flow plots for all altitudes. Three G levels were considered (0.8, 1.0, and 1.2). In addition, for G = 1.0, a more negative Base Excess (actual Base Excess – 6 mEq/l) was also considered to simulate the presence of lactic acid. A strong dependance of the functions on G, and thus on the shape of the OEC, can be observed under all conditions, especially so at higher altitudes, for the single leg compartment, and for increasing PO_2 values.

Discussion

The model, although restrictive, needs some assumptions.

1. The mass conservation principle is assumed to hold true under all investigated conditions. Hence the Fick equation was taken to represent the dependency of blood flow on [Hb], VO_2, and venous and arterial gas composition, and the Henderson-Hasselbalch equation was taken to represent the dependency of the total CO_2 content on pH and PCO_2, respectively.

Table 1. Values used for the simulations.

Alt. m.	B.P. torr	VO_2 whole body l/min	VO_2[a] one leg l/min	[Hb] g/dl	Base Excess mEq	PO_2 arterial torr	PCO_2 arterial torr
0	760[b]	4.63[g]	1.56	14.5[c]	0[c]	95[c]	40[c]
3850	485[d]	3.70[d]	1.24	17.6[d]	−3[c]	50[c]	31[e]
5400	400[b]	2.87[f]	0.96	18.4[c]	−5[f]	38[f]	20[f]
6300	351[b]	2.31[g]	0.78	18.4[c]	−7[c]	31[c]	18.4[c]
8848	253[b]	1.07[g]	0.36	18.4[c]	−7[c]	22[c]	7.5[c]

[a] Jorfeldt and Wahren, 1971. [b] West et al., 1983a. [c] Winslow et al., 1984. [d] Samaja et al., 1979. [e] Unpublished observations. [f] Cerretelli, 1976. [g] West et al., 1983b.

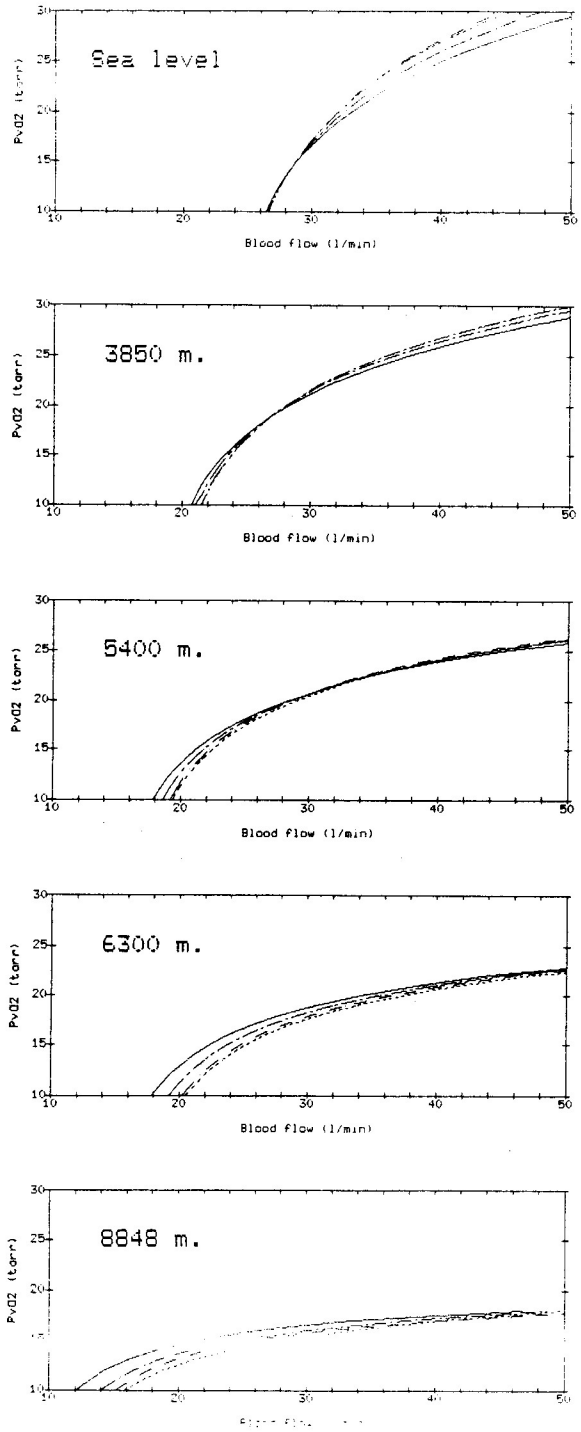

Fig. 1. Venous PO_2 vs. blood flow for the whole body at the various altitudes indicated in the figure, at G = 0.8 (single), 1.0 (dotdash), 1.2 (dot), and G = 1.0 with Base Excess 6 mEq lower than that reported in table 1 (dash). The other values used for the simulations are listed in Table 1.

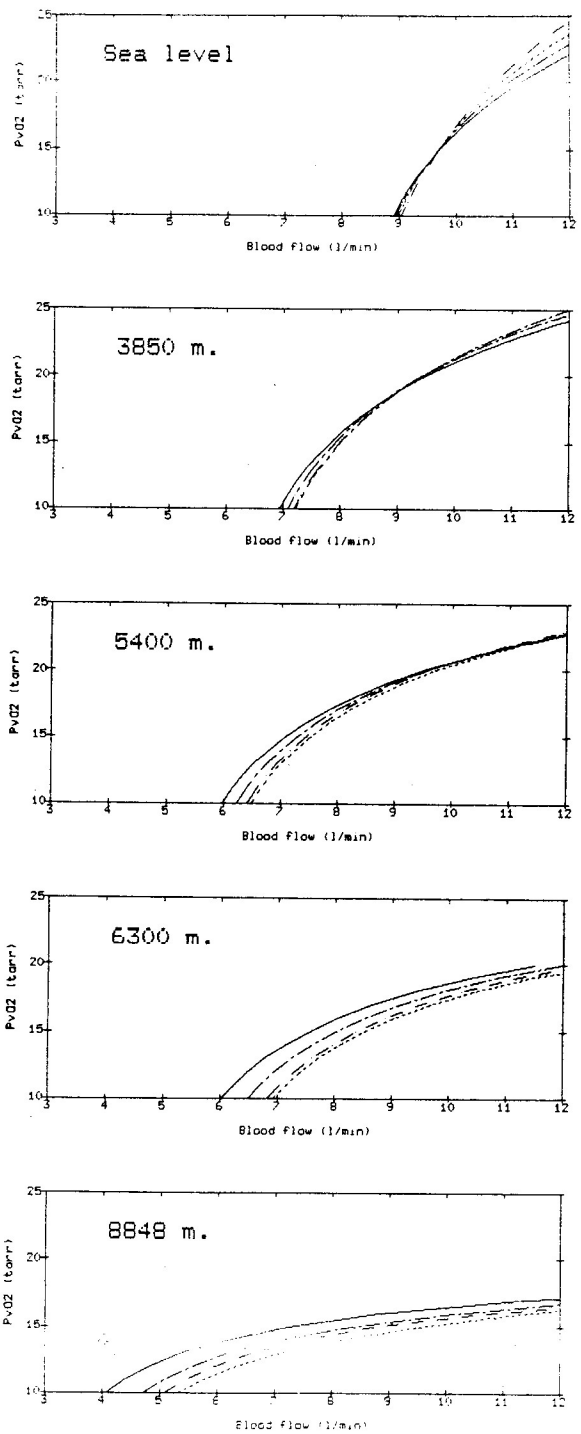

Fig. 2. Same as in Fig. 1, but for one leg.

2. Venous and arterial blood Base Excess are assumed to be equal, thus the concentration of lactic acid in arterial and venous blood is the same; this implies that all simulations are performed under apparently steady-state conditions.

3. No temperature gradient is assumed to exist between arterial and venous blood.

4. No additional factors for the modulation of the oxygen affinity, besides pH, PCO_2 and G are postulated.

Venous PO_2 vs. blood flow relationships are strongly dependent on G and on Base Excess, which affect the oxygen transport via their modulation of the OEC. The effects of the above factors on the oxygen transport are markedly increased for increasing altitudes, and when considering the local compartment instead of the whole body. Although it is rather difficult to assess if there is an optimal set for each altitude, a lower blood flow at a given venous PO_2 and constant values for the other parameters is considered advantageous because it implies a minor load for the heart and the circulation in general, and thus a more efficient oxygen transport. Therefore, it seems that the advantages of a rightward shift of the OEC, no matter if mediated by G or by pH, are strongly dependent on altitude. In fact, the general trend of the oxygen transport as a function of few selected hematologic factors clearly indicates a positive effect of a rightward shift of the OEC for altitudes <5400 m, and for relatively high PO_2 values, as is the case during moderate metabolic loads. At extreme altitudes, on the contrary, and at heavy exercise, a rightward shift of the OEC may be regarded too as a maladaptive response.

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