Respiration Physiology (1986) 64, 191–202
Elsevier

THE ROLE OF 2,3-DPG IN THE OXYGEN TRANSPORT AT ALTITUDE

MICHELE SAMAJA[1], PIETRO E. DI PRAMPERO[2] and PAOLO CERRETELLI[2]

[1]Dipartimento di Scienze e Tecnologie Biomediche, Università degli Studi di Milano, via Olgettina 60, 20132 Milano, Italy; and [2]Département de Physiologie de l'Université, C.M.U., 1 rue Michel Servet, 1211 Geneve 4, Switzerland

Abstract. A computer program is described, relating blood flow with venous P_{O_2} for any given set of the following parameters: oxygen uptake, respiratory quotient, the 2,3-DPG/Hb molar concentration ratio (G), arterial P_{O_2}, P_{CO_2}, and pH. Two compartments (total body and one leg) and two conditions (rest and maximal exercise) are considered. Calculations are performed at five altitudes (0, 3850, 5400, 6300 and 8848 m), for which the above variables are known. The results indicate that an increased G value has a negative effect on the oxygen delivery to tissues at very high altitudes (> 5400 m), irrespectively of the work load, since larger blood flows ($\Delta\dot{Q}$ on the summit of Mt. Everest is + 4 to + 7 l/min, and + 1 to + 2.5 l/min, for whole body and one leg, respectively) are required for a given oxygen uptake. For submaximal work at altitudes ranging from sea level up to 5400 m, as well as for moderate work at 5400 m, high G values improve the oxygen delivery to tissues.

Altitude	2,3-DPG	Oxygen dissociation curve
Blood	Exercise	Oxygen transport

Intraerythrocytic concentration of 2,3-diphosphoglycerate (DPG, see table 1 for other abbreviations), a strong effector of hemoglobin oxygenation (Benesch and Benesch, 1967), and blood pH were found to increase (blood base excess decreases) in man exposed to extreme hypoxia (Winslow *et. al.*, 1984). The same authors also showed that the effect of pH largely offsets the opposite effect of DPG, leading to an increased blood oxygen affinity (P_{50} = 19.4 Torr at 8848 m, in comparison to 28.1 Torr at sea level). It is rather controversial whether a leftward shift of the oxygen equilibrium curve (OEC) is beneficial or not for the oxygen transport from lungs to tissues. Most textbooks (see, for a review, Lambertsen, 1974b; Keele *et. al.*, 1982; Ulmer, 1983), as well as some authors (Aste Salazar and Hurtado, 1944; Lenfant *et al.*, 1968; Eaton *et al.*, 1969; Frisancho, 1975), point out that an increased DPG concentration, and thus a decreased blood oxygen affinity, is an adaptive response to hypoxia. More recent work (Torrance

Accepted for publication 3 January 1986

0034-5687/86/$03.50

et al., 1970/71; Lenfant *et al.*, 1971; Weiskopf and Severinghaus, 1972) has suggested this effect to be less important than presumed. Finally, the advantages of an increased blood oxygen affinity at moderate to extreme hypoxia have been shown both theoretically (Mitchell *et al.*, 1972; Turek *et al.*, 1973; West and Wagner, 1980; Bencowitz *et al.*, 1982; Willford *et al.*, 1982), and experimentally on rats (Eaton *et al.*, 1974; Turek *et al.*, 1978) and on humans (Hebbel *et al.*, 1978). All these studies, however, were unable to separate the opposite effects of pH and DPG on the modulation of the OEC, and thus on the oxygen delivery to tissues.

In this work, a new approach is reported to predict the changes of the oxygen transport properties that are induced by changes of the blood oxygen affinity, both at rest and at exercise, and at varying altitudes ranging from sea level to the summit of Mt. Everest (8848 m). This approach calculates blood OEC as a continuous function of pH, P_{CO_2}, and DPG (Winslow *et al.*, 1983), in order to define a steady-state relationship between the venous P_{O_2} and the blood flow necessary to transport a given amount of oxygen at constant values for the other parameters. To override difficulties due to the assumption that all districts of the organism have the same average oxygen consumption, and since central venous P_{O_2} and cardiac output might not be reliable indexes to assess the oxygen transport characteristics of specific compartments such as working muscles, we will also consider the oxygen transport in one leg, where venous P_{O_2} and blood flow can be assumed to represent capillary P_{O_2} and local blood flow, respectively.

Theory

A computer program was devised which uses the following routines:

(1) Prediction of blood OEC from pH, P_{CO_2}, and the [2,3-DPG]/[Hb] molar ratio (G) (Winslow *et al.*, 1983), and of S_{O_2} from P_{O_2};

(2) Calculation of BE from [Hb], P_{CO_2}, [DPG], pH, and S_{O_2} (Thomas, 1972);

(3) Solution of the Fick equation in the forms:
$\dot{Q} = \dot{V}c_{O_2}/[Hb] \cdot 0.0134 \cdot (Sa_{O_2} - S\bar{v}_{O_2}) + a_{O_2} \cdot 22.4 \cdot (Pa_{O_2} - P\bar{v}_{O_2})$
or
$\dot{q} = \dot{V}l_{O_2}/[Hb] \cdot 0.0134 \cdot (Sa_{O_2} - Sv_{O_2}) + a_{O_2} \cdot 22.4 \cdot (Pa_{O_2} - Pv_{O_2})$
(Severinghaus, 1971), where a_{O_2} is calculated as a function of temperature (Roughton and Severinghaus, 1973);

(4) Calculation of Ct_{CO_2} from P_{CO_2} and pH, by the Henderson-Hasselbalch formula:
$Ct_{CO_2} = (a_{CO_2} \cdot P_{CO_2}) \cdot [1 + 10^{(pH - pK)}]$,
where $a_{CO_2} = 0.0306$ at 37 °C (Severinghaus, 1971), and pK is calculated as:
$pK = 6.099 - 0.04167 \cdot (pH - 7.4)$
(Severinghaus, 1971);

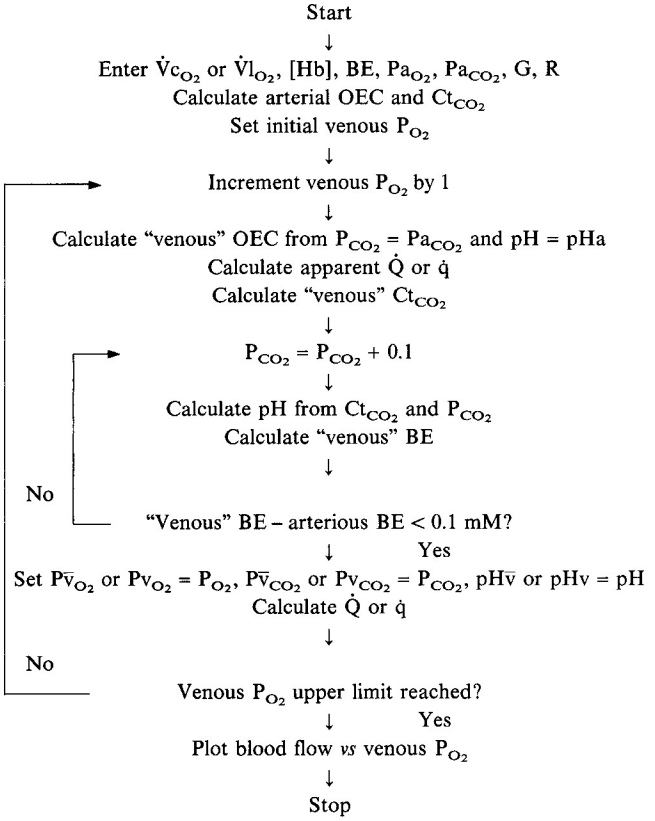
(5) Estimation of the amount of excreted CO_2 for a given amount of consumed O_2 from R.

The flowchart is shown in table 2 and explained in detail later. The aim of the

TABLE 1
List of abbreviations and of units.

Abbreviation	Full name	Unit
aCO_2	CO_2 solubility	mM/torr
aO_2	O_2 solubility	mM/torr
BE	Base excess	mM
Ct_{CO_2}	Total CO_2 content	mM
DPG	2,3-diphosphoglycerate	mM
G	[DPG]/[Hb]	M/M
[Hb]	Hemoglobin concentration	g/dl
Pb	Barometric pressure	Torr
$\dot{Q}$	Blood flow (central)	l/min
$\dot{q}$	Blood flow (leg)	l/min
R	Gas exchange ratio	–
S_{O_2}	Oxygen saturation	–
$\dot{V}c_{O_2}$	Oxygen consumption (central)	l/min
$\dot{V}l_{O_2}$	Oxygen consumption (leg)	l/min

TABLE 2
Program flowchart.



program is to define a relationship between venous P_{O_2} and blood flow at constant values for the independent variables.

The system is based on the following assumptions:

(1) O_2 and CO_2 are involved in respiration processes only;
(2) The classical Fick and Henderson-Hasselbalch equations are valid and sufficient to describe the dependency of blood flow on [Hb], $\dot{V}_{O_2}$ and venous and arterial gas compositions, and that of Ct_{CO_2} on pH and P_{CO_2}, respectively;
(3) Venous blood BE is the same as arterial blood BE, *i.e.*, the distribution of cations inside and outside the red cell, and the concentration of lactic acid are the same in arterial and venous blood;
(4) The equations to predict OEC are valid under all circumstances.

The FORTRAN program runs on a Digital PRO 350 personal computer, and starts with the input of [Hb], G, O_2 and CO_2 partial pressures in arterial blood, BE, R, and $\dot{V}c_{O_2}$ or $\dot{V}l_{O_2}$. Plasma protein concentration and temperature are set, respectively, to 70 g/l and 37 °C. These data are sufficient to define arterial pH, OEC and Sa_{O_2}. Then, the following calculations are iterated by increasing venous P_{O_2} by 1 Torr steps in an appropriately selected range.

Venous P_{CO_2} and pH are estimated in the following way. First, their initial values are set equal to the arterial ones, and P_{CO_2} is iteratively increased by 0.1 Torr steps. At each iteration, the apparent venous OEC is computed, and hence the blood flow ($\dot{Q}$ or $\dot{q}$) necessary to transport a fixed amount of oxygen ($\dot{V}c_{O_2}$ or $\dot{V}l_{O_2}$) is evaluated as a function of that OEC. The value for Ct_{CO_2} can therefore be calculated from R, and hence the apparent 'venous' BE, which is compared to the arterial one. If the two values do not match within a predefined range (usually $\pm$ 0.1 mM), another iteration takes place.

Iterations stop when venous and arterial BE are coincident, and the program uses the current P_{CO_2} and pH to calculate the true venous OEC. The blood flow required to yield the imposed $\dot{V}_{O_2}$ can thus be calculated from a set of Pv_{O_2} values 1 Torr apart. Data are finally plotted as $P\bar{v}_{O_2}$ or Pv_{O_2} *vs* $\dot{Q}$ or $\dot{q}$.

Results

Table 3 shows the values used for the simulations and their sources. When possible, experimentally defined values were used, with the exception of R, because the value of 1.2 reported on the summit of Mt. Everest (West *et al.*, 1983a) may be indicative of a non-steady state condition, as pointed out by the authors. Therefore, we used for all altitudes the theoretical values of 0.8 and 1.0 for rest and maximal work conditions, respectively.

When the central compartment was considered, $\dot{V}c_{O_2}$ is intended as the total oxygen consumption of the body, $\dot{Q}$ as cardiac output, and $P\bar{v}_{O_2}$ as mixed venous P_{O_2}. Instead, when considering the local compartment (the leg), $\dot{V}l_{O_2}$ is intended as the oxygen consumed in that leg, $\dot{q}$ as the blood flow in the leg, and Pv_{O_2} as the P_{O_2} in the femoral

TABLE 3
Values used for the simulations.

Alt.	Metab. rate	Pb	$\dot{V}c_{O_2}$	$\dot{V}l_{O_2}$ [a]	[Hb]	BE	Pa_{O_2}	Pa_{CO_2}
0	Rest	760[b]	0.35[c]	0.03	14.5	0[d]	95[d]	40[d]
	Work		4.63[i]	1.56				
3850	Rest	485[f]	0.35[c]	0.03	17.6[f]	− 3[g]	50[g]	31[g]
	Work		3.70[f]	1.24				
5400	Rest	400[b]	0.35[c]	0.03	18.4[d]	− 5[h]	41[h]	20[h]
	Work		2.87[h]	0.96			38[h]	
6300	Rest	351[b]	0.35[c]	0.03	18.4[d]	− 7[d]	39[d]	18.4[d]
	Work		2.31[i]	0.78			31[d]	
8848	Rest	253[b]	0.35[c]	0.03	18.4[d]	− 7[d]	28[d]	7.5[d]
	Work		1.07[i]	0.36			22[d]	

[a] Veicsteinas *et al.*, 1984; [b] West *et al.*, 1983a; [c] Robinson, 1974; [d] Winslow *et al.*, 1984; [e] Lambertsen, 1974a; [f] Samaja *et al.*, 1979; [g] Unpublished observations; [h] Cerretelli, 1976; [i] West *et al.*, 1983b.

vein. Single leg $\dot{V}_{O_2}$ was interpolated (Veicsteinas *et al.*, 1984) from actual data (Jorfeldt and Wahren, 1971; Pernow *et al.*, 1965).

Simulations are performed at three G values (which is therefore an independent variable). Some are also performed at more negative BE values (actual BE value − 6 mM) to simulate the presence of lactic acid. Five different altitudes, *i.e.*, 0, 3850, 5400, 6300, and 8848 m were considered throughout. Their choice was mainly driven by the availability of homogeneous data. For each altitude, for each metabolic level, and for each compartment, a venous P_{O_2} *vs* $\dot{Q}$ or $\dot{q}$ plot was obtained.

Figure 1 shows the venous P_{O_2} *vs* blood flow ($\dot{Q}$) plot for the central compartment (upper and lower panel, rest and nearly maximal work, respectively) at the two extreme altitudes. Figure 2 shows the same plots for the local compartment (leg).

Discussion

As outlined in the theory section, the system needs some assumptions:

(1) The equality of BE (and thus of lactic acid concentration) in arterial and venous blood;
(2) Steady-state conditions;
(3) The validity of the procedure used for calculating the OEC; and
(4) The absence of a temperature gradient between arterial and venous blood.

Whereas assumptions (1) and (2) seem reasonable and therefore were also the key to extrapolate maximal $\dot{V}_{O_2}$ on the summit of Mt. Everest (West *et al.*, 1983a), the possible role of (3) and (4) is discussed below.

The prediction of OEC from pH, P_{CO_2} and G using the reported equations (Winslow *et al.*, 1983) is validated by the observation that the P_{50} values reported on climbers

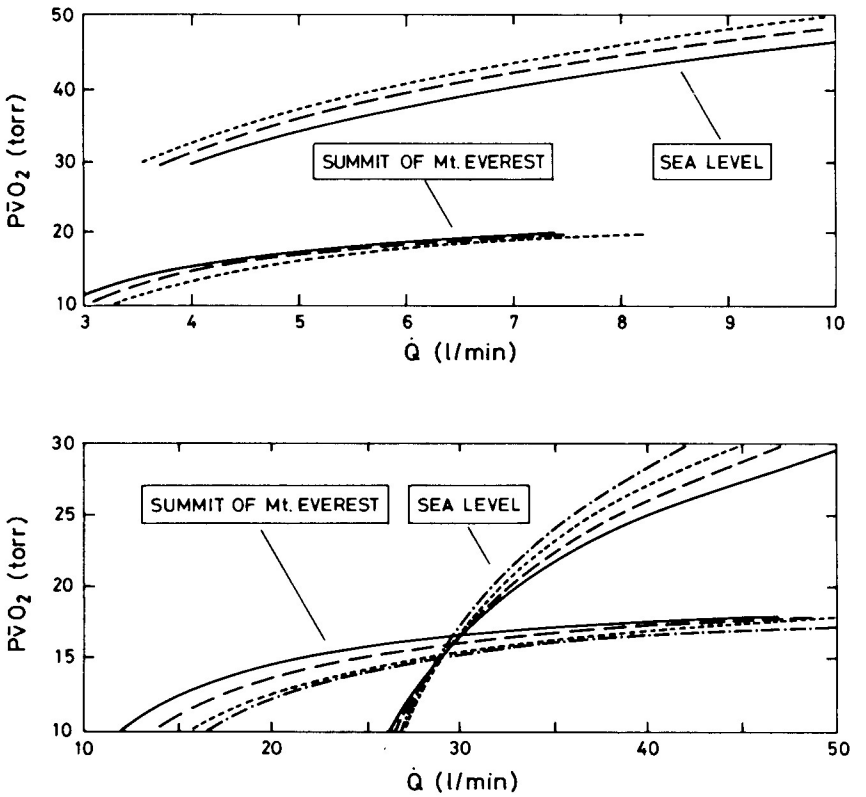


Fig. 1. $P\bar{v}_{O_2}$ *vs* $\dot{Q}$ at rest (upper panel) and at work (lower panel), for whole body, at G = 0.8 (continuous line), 1.0 (dashed line), and 1.2 (dotted line). The values for the other parameters are listed in table 3. The dotted–dashed line in the lower panel represents a BE value of 6 mM more negative than that shown in table 3 at G = 1.0.

(Winslow *et al.*, 1984) match very well with those calculated from pH, P_{CO_2}, and G (Samaja *et al.*, 1981), indicating that no additional factors for the modulation of the oxygen affinity need to be postulated. Partially inaccurate results may however derive from P_{CO_2} and pH values exceeding the recommended range (such as on the summit of Mt. Everest). On the other hand, no approach we are presently aware of can handle OECs under such extreme conditions.

The oxygen transport was also computed in a single compartment (one leg) since mixed venous P_{O_2} and cardiac output might not be adequate indexes of the oxygen transport to the working muscles. Indeed, when dealing with one compartment only, the assumption that all districts under investigation have the same O_2 consumption and venous P_{O_2} seems closer to the truth.

In spite of the possible inaccuracies, figs. 1 and 2 show that the Pv_{O_2} *vs* blood flow relationships are strongly dependent on G and on BE, the Pv_{O_2} difference for a given blood flow being greater at work, at altitude, and when considering the local compart-

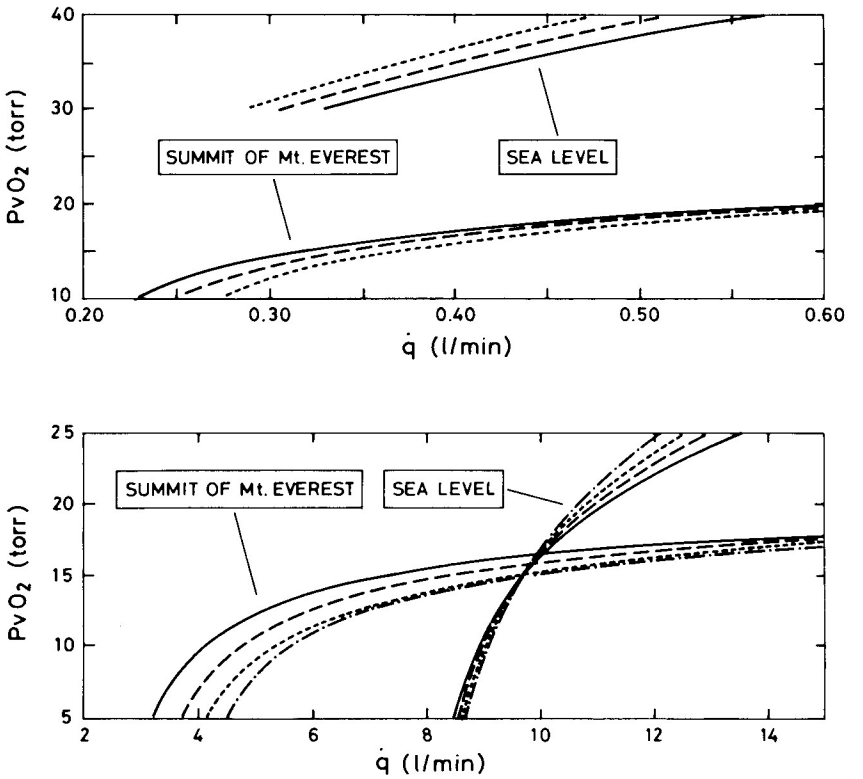


Fig. 2. Same as in fig. 1 for the leg compartment.

ment. Figure 3 reports, at all considered altitudes, the horizontal algebraic difference in blood flow, at constant venous P_{O_2} between the curves referring to G = 1.2 and 0.8, a positive difference indicating that a G increase from 0.8 to 1.2 implies a larger blood flow. If the difference is negative, the opposite is true.

It is rather difficult to establish what the optimal conditions are at a given altitude; however, if a lower blood flow at a given venous P_{O_2} and constant values of the other parameters is considered advantageous, then the same increase of G, while being positive at sea level, is more and more disadvantageous as the altitude increases.

The explanation of this phenomenon depends on the form of the OEC (fig. 4). At sea level, where Pa_{O_2} and Pv_{O_2} are relatively high, a P_{50} increase from 27.9 to 31.4 Torr, induced by an increase of G from 0.8 to 1.2 (pH 7.4, P_{CO_2} 40 Torr), results in an increase of the artero-venous oxygen difference from 3.64 to 4.24 mM [O_2] ([Hb] = 14.5 g/dl). Instead, at 8848 m, where Pa_{O_2} and Pv_{O_2} are relatively low, for the same increase of G, which shifts P_{50} from 22.1 to 27.9 (pH 7.55, P_{CO_2} 7.5 Torr), the artero-venous difference falls from 4.11 to 3.00 mM [O_2] ([Hb] = 18.4 g/dl). It is therefore evident that when the arterial and venous points are in the higher P_{O_2} range, a shift of the OEC to the right increase the artero-venous difference for a given P_{O_2} change, because the

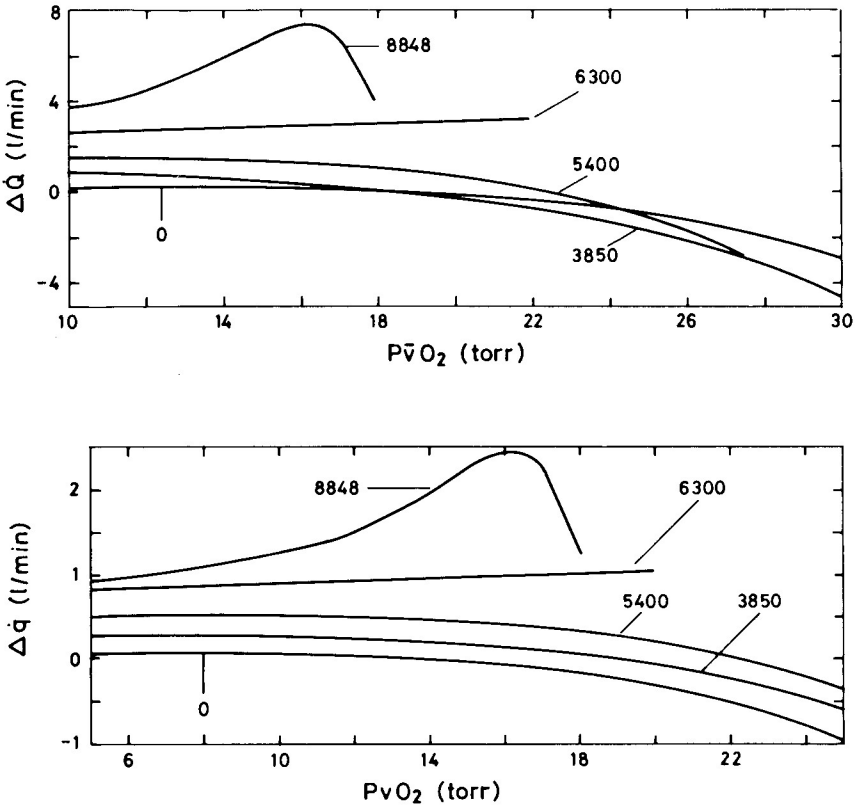


Fig. 3. Blood flow horizontal difference (blood flow at G = 1.2) – (blood flow at G = 0.8, as from figs. 1 and 2) *vs* venous P_{O_2} for whole body (upper panel) and one leg (lower panel), at the indicated altitudes. On the basis of known $P\bar{v}_{O_2}$ and Pv_{O_2} values, it may be predicted that up to 5400 m an increased G ratio is favourable, particularly at rest and moderate work load.

gain in the oxygen released to the tissues exceeds the loss of the oxygen bound in the lungs. The opposite is true when Pa_{O_2} and Pv_{O_2} are in the lower P_{O_2} range.

A major source of inaccuracies in this treatment of data derives from assuming a constant 37 °C temperature. While the effect of temperature on human blood P_{50} is well known (Samaja *et al.*, 1983), few data are up to now available to account for the combined effect of temperature with G, pH, P_{CO_2} on the shape of the OEC and the Adair constants. Therefore the prediction of the OEC and, as a consequence, of the oxygen transport at varying temperatures is arbitrary, especially when considering all the side effects of thermic change of the red cell, such as: (i) the new equilibrium between dissolved and bound O_2; (ii) the new equilibrium between dissolved CO_2, bicarbonate and carbonates; (iii) the new equilibrium between intra- and extra-cellular protons. Simulating the oxygen transport with these uncertainties may lead to quite inaccurate results. However, as a first approximation, a temperature gradient between arterial and

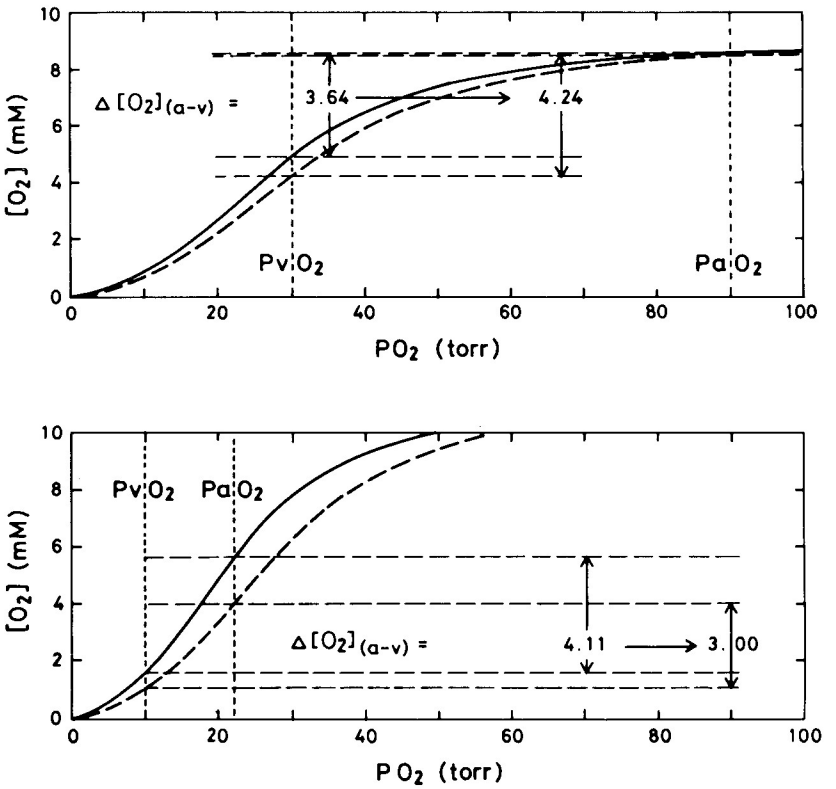


Fig. 4. The OEC at sea level (upper panel, pH = 7.4, P_{CO_2} = 40 Torr, [Hb] = 14.5 g/dl) and on the summit of Mt. Everest (lower panel, pH 7.55, P_{CO_2} = 7.5, [Hb] = 18.4 g/dl). The leftmost and the rightmost curves are drawn at G = 0.8 and 1.2, respectively.

venous blood may be considered in the same way as a gradient of G (a temperature increase of 3 °C has approximately the same effect on P_{50} as an increase of G from 0.8 to 1.2). Figure 5 shows the effect of a 3 °C temperature gradient between arterial and venous blood on the Pv_{O_2} *vs* $\dot{q}$ plot for one leg at sea level and at extreme altitudes. It can be seen that a peripherally increased temperature (as in working muscle) enhances oxygen delivery because it favours the release of oxygen from hemoglobin to tissues.

We are fully aware that the oversimplifications inherent in the above treatment do not allow an exact prediction of the oxygen transport at altitude. Indeed, many important factors, such as the improved capillarization, the pulmonary shunt, the permeability of lung membrane to gases, the changes of blood viscosity and many others could not be measured nor considered. Nevertheless, the general trend of the oxygen transport as a function of few selected hematologic factors clearly indicates a negative effect of a rightward shift of the OEC. This seems to be true, however, only for very high to extreme altitudes. Indeed, fig. 3 shows that, when considering only altitudes < 5400 m, and for relatively high P_{O_2} values, as in the case during moderate metabolic loads, an increase

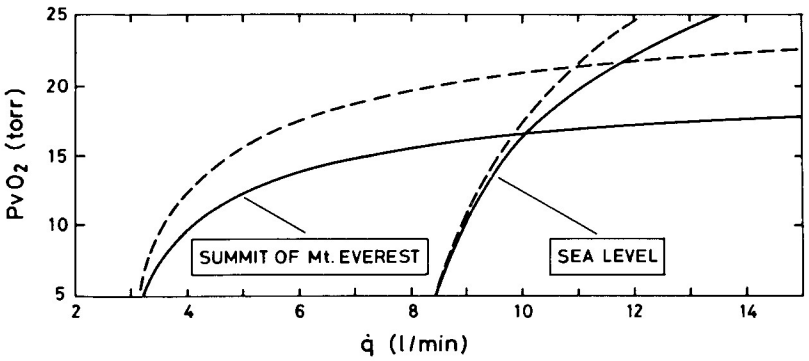


Fig. 5. Pv_{O_2} *vs* $\dot{q}$ plot simulating a + 3 °C temperature gradient (dotted line), and no gradient (continuous line). The temperature gradient was simulated by imposing a G value of 0.8 and 1.2 in arterial and venous blood, respectively.

of G has a favourable effect in so far as it allows a given O_2 consumption with a reduced blood flow.

Recent experimental work is consistent with these theoretical conclusions. Eaton *et al.* (1974) reported the protective effect of an increased blood oxygen affinity, obtained by pre-treatment with sodium cyanate, on rats exposed to acute extreme hypoxia (Pb = 233 Torr for 90 min). Turek *et al.* (1978) reported that cyanate-treated rats breathing low oxygen mixtures had lower venous P_{O_2} and better survival in respect to controls. Both studies, however, were performed on blood with relatively low oxygen affinity (P_{50} > 37 Torr) and failed to account for a gradual acclimatization as is the case in mountaineering. Hebbel *et al.* (1978) showed the advantages of left shifted OEC (P_{50} = 17 Torr) in two subjects with Hb Andrew-Minneapolis ($\beta^{144\ Lys \rightarrow Asn}$), in comparison with their siblings with normal Hb, at an altitude of 3100 m. Our data, however, failed to support their conclusion at such low altitudes.

Most theoretical studies about OEC and the oxygen transport were performed using the well-known Bohr integration, without accounting for the fine modulation of the OEC on the oxygen delivery system. For example, Mitchell *et al.* (1972) did not allow venous P_{O_2} (and thus venous S_{O_2}) to change as function of oxygen uptake. Turek *et al.* (1973) have studied the effect of the same P_{50} change, no matter whether due to DPG or pH changes, on venous P_{O_2} at an oxygen uptake simulating a resting condition, while it is shown in this work that the same DPG increase may lead to quite different OECs depending on altitude. In their prediction of gas exchange on the summit of Mt. Everest, West and Wagner (1980) pointed out the positive effect of a left shifted OEC on oxygen transport. They had to assume, however, a complete compensation at lower altitude, and could not evaluate the intermediate altitudes between 0 and 8848 m, due to the lack of sufficient data. Finally, Bencowitz *et al.* (1982) have based their calculations only on 3 OECs (P_{50} = 16.8, 26.8, 36.8 Torr) at 4 altitudes up to 5800 m, without considering that at each altitude a peculiar OEC occurs. Willford *et al.* (1982) analyzed the optimal position of the OEC in order to maximize artero-venous difference, but failed to explain

the dependence of venous P_{O_2} on the OEC itself, and how physiological variables (for example blood flow) can compensate a non optimal OEC. Our data are nevertheless consistent with the general conclusions of these authors, stressing however that the shifts of the OEC at altitude, due to the combined change of pH and DPG, or also at sea level for high metabolic rates, are much more important than generally recognized.

In conclusion, we would like to point out again that, at altitudes < 5400 m the observed increase of G may be considered advantageous in terms of O_2 delivery to tissues during everyday life for moderate physical activity and particularly at rest. Only at extreme altitudes and at very heavy exercise, *i.e.*, in rather unusual situations, does the increase of G become a maladaptive response.

References

Aste-Salazar, H. and A. Hurtado (1944). The affinity of hemoglobin for oxygen at sea level and at high altitudes. *Am. J. Physiol.* 142: 733–743.

Bencowitz, H.Z., P.D. Wagner and J.B. West (1982). Effect of change in P_{50} on exercise tolerance at high altitude: a theoretical study. *J. Appl. Physiol.* 53: 1487–1495.

Benesch, R. and R.E. Benesch (1967). The effect of organic phosphates from human erythrocyte on the allosteric properties of human hemoglobin. *Biochem. Biophys. Res. Commun.* 26: 659–667.

Cerretelli, P. (1976). Limiting factors to oxygen transport on Mount Everest. *J. Appl. Physiol.* 40: 658–667.

Eaton, J.W., G.J. Brewer and R.F. Groover (1969). Role of red cell 2,3-diphosphoglycerate in the adaptation of man to altitude. *J. Lab. Clin. Med.* 73: 603–609.

Eaton, J.W., T.D. Skelton and E. Berger (1974). Survival at extreme altitude: protective effect of an increased hemoglobin-oxygen affinity. *Science* 183: 743–744.

Frisancho, A.R. (1975). Functional adaptation to high altitude hypoxia. *Science* 187: 313–319.

Hebbel, R.P., J.W. Eaton, R.S. Kronenberg, E.D. Zanjani, L.G. Moore and E.M. Berger (1978). Human llamas. Adaptation to altitude in subjects with high hemoglobin oxygen affinity. *J. Clin. Invest.* 62: 593–600.

Jorfeldt, L. and J. Wahren (1971). Leg blood flow during exercise in man. *Clin. Sci.* 41: 459–473.

Keele, C.A., E. Neil and N. Joels (1982). Samson Wright's Applied Physiology, 13th edition. New York, Toronto, Oxford University Press, pp. 185–186.

Lambertsen, C.J. (1974a). The atmosphere and gas exchanges with the lungs and blood. In: Medical Physiology, 13th edition, edited by V.B. Mountcastle. St. Louis, The C.V. Mosby Company, pp. 1372–1398.

Lambertsen, C.J. (1974b). Anoxia, altitude, and acclimatization. In: Medical Physiology, 13th edition, edited by V.B. Mountcastle. St. Louis, The C.V. Mosby Company, pp. 1538–1562.

Lenfant, C., J.D. Torrance, E. English, C.A. Finch, C. Reynafarje, J. Ramos and J. Faura (1968). Effect of altitude on oxygen binding by hemoglobin and on organic phosphate levels. *J. Clin. Invest.* 47: 2652–2656.

Lenfant, C., J.D. Torrance and C. Reynafarje (1971). Shift of the O_2-Hb dissociation curve at altitude: mechanism and effect. *J. Appl. Physiol.* 30: 625–631.

Mitchell, J.H., K. Wildenthal and R.J. Johnson (1972). The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney Int.* 1: 375–389.

Pernow, B., J. Wahren and S. Zetterquist (1965). Studies on peripheral circulation and metabolism in man. *Acta Physiol. Scand.* 64: 289–298.

Robinson, S. (1974). Physiology of muscular exercise. In: Medical Physiology, 13th edition, edited by V.B. Mountcastle. St. Louis, The C.V. Mosby Company, pp. 1273–1304.

Roughton, F.J.W. and J.W. Severinghaus (1973). Accurate determination of oxygen dissociation curve of human blood above 98.7% saturation with data on oxygen solubility in unmodified human blood from 0 °C to 37 °C. *J. Appl. Physiol.* 35: 861–869.

Samaja, M., A. Veicsteinas and P. Cerretelli (1979). Oxygen affinity of blood in altitude Sherpas. *J. Appl. Physiol.* 47: 337–341.

Samaja, M., A. Mosca, M. Luzzana, L. Rossi-Bernardi and R.M. Winslow (1981). Equations and nomogram for the relationship of human blood P_{50} to 2,3-diphosphoglycerate, CO_2, and H^+. *Clin. Chem.* 27: 1856–1861.

Samaja, M., D. Melotti, E. Rovida and L. Rossi-Bernardi (1983). Effect of temperature on the P_{50} value for human blood. *Clin. Chem.* 29: 110–114.

Severinghaus, J.W. (1971). Carbon dioxide solubility and first dissociation constant (pK′) of carbonic acid in plasma and cerebrospinal fluid: man. In: Respiration and Circulation, edited by P.L. Altman and D.S. Dittmer. Bethesda, MD., Fed. Am. Soc. Exptl. Biol., pp. 218–219.

Thomas, L.J. (1972). Algorithms for selected blood acid-base and blood gas calculations. *J. Appl. Physiol.* 33: 154–158.

Torrance, J.D., C. Lenfant, J. Cruz and E. Marticorena (1970/1971). Oxygen transport mechanism in resident at high altitude. *Respir. Physiol.* 11: 1–15.

Turek, Z., F. Kreuzer and L.J.C. Hoofd (1973). Advantage or disadvantage of a decrease of blood oxygen affinity for tissue oxygen supply at hypoxia. *Pflügers Arch.* 342: 185–197.

Turek, Z., F. Kreuzer and E.M. Ringnalda (1978). Blood gases at several levels of oxygenation in rats with a left shifted blood oxygen dissociation curve. *Pflügers Arch.* 376: 7–13.

Ulmer, H.V. (1983). Work physiology; environmental physiology. In: Human Physiology, edited by R.F. Schmidt and G. Thews. Berlin, Heidelberg, New York, Springer-Verlag, pp. 548–572.

Veicsteinas, A., M. Samaja, M. Gussoni and P. Cerretelli (1984). Blood oxygen affinity and maximal oxygen consumption in élite bicycle racers. *J. Appl. Physiol.* 57: 52–58.

Weiskopf, R.B. and J.W. Severinghaus (1972). Lack of effect of high altitude on hemoglobin oxygen affinity. *J. Appl. Physiol.* 33: 276–277.

West, J.B. and P.D. Wagner (1980). Predicted gas exchange on the summit of Mt. Everest. *Respir. Physiol.* 42: 1–16.

West, J.B., S.J. Boyer, D.J. Graber, P.H. Hackett, K.H. Maret, J.S. Milledge, R.M. Peters, C.J. Pizzo, M. Samaja, F.H. Sarnquist, R.B. Schoene and R.M. Winslow (1983a). Maximal exercise at extreme altitudes on Mount Everest. *J. Appl. Physiol.* 55: 688–698.

West, J.B., S. Lahiri, K.H. Maret, R.M. Peters and C.J. Pizzo (1983b). Barometric pressure at extreme altitudes on Mount Everest: physiological significance. *J. Appl. Physiol.* 54: 1188–1194.

Willford, D.C., E.P. Hill and W.Y. Moores (1982). Theoretical analysis of optimal P_{50}. *J. Appl. Physiol.* 52: 1043–1048.

Winslow, R.M., M. Samaja, N.J. Winslow, L. Rossi-Bernardi and R.I. Shrager (1983). Simulation of continuous blood oxygen equilibrium curve over physiological pH, DPG, and P_{CO_2} range. *J. Appl. Physiol.* 54: 524–529.

Winslow, R.M., M. Samaja and J.B. West (1984). Red cell function at extreme altitude on Mount Everest. *J. Appl. Physiol.* 56: 109–116.