Blood gas transport at high altitude

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Abstract

As a model of human hypoxia, exposure to high-altitude causes a number of ventilatory, circulatory and hemopoietic adaptations. A review of literature on blood-gas transport responses to hypoxia indicates that they are influenced not only by altitude, but also by factors related to acclimatization. In addition, it appears that the need to oxygenate tissues conflicts with the need to maintain H^+ homeostasis. Thus, the final situation represents a compromise between the respiratory adjustment aimed at increasing blood alkalosis in order to optimize the oxygen transport system, and the metabolic readjustment aimed at re-establishing normal blood pH. There are factors like red cell 2,3-diphosphoglycerate, a compound that decreases the hemoglobin affinity for oxygen, that can influence that balance by affecting arterial oxygen saturation through mechanisms independent of respiration.

Introduction

Exposure to high altitude is associated to a number of physiological and pathological responses. The first description of the deleterious effects of high altitude on humans seems to date back to 30 B.C., when Tseen Han Shoo so described the journey along the Silk Road in Karakorum: “The route from the Western regions to the Hindu Kush crosses the Great Headache mountain, the Little Headache mountain, [where] men’s body become feverish, lose color, and are attached with headache and vomiting” [1]. Since the 19th century, with the studies by Paul Bert, it is appreciated that altitude problems stem out from the decreased barometric pressure, hence hypoxia.

If adaptation is defined as a change that reduces the physiological strain produced by stressful aspects of the environment [2], it is either genotypic or phenotypic [3]. In the latter case, it is also termed “acclimatization” [4]. Humans can adapt to hypoxia, although less extensively than other mammals do [5], by establishing some degree of compensation at several levels [6-8]. Briefly, at *ventilatory level*, hypoxic stimulation of chemoreceptors causes an immediate increase of alveolar ventilation. The consequent washout of large quantities of CO_2 initially reduces arterial CO_2 tension (P_aCO_2[†]) and

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[†] ¶ List of abbreviations: AMS; acute mountain sickness; BE, base excess; DPG, 2,3-diphosphoglycerate; Hb, hemoglobin; OEC, O_2 equilibrium curve; P_aCO_2, arterial CO_2 tension; P_aO_2, arterial O_2 tension; pH_a, arterial pH; P_vO_2, venous O_2 tension; P_{50}, PO_2 at

increases arterial pH (pH_a). Subsequently, whereas the chemoreflexogenic hyperventilatory response remains unchanged, pH_a tends to return to near normal levels as a consequence of HCO_3^- loss through the kidney. At *circulatory level*, hypoxia increases circulatory efficiency by three mechanisms: (1) immediate increase in cardiac output, followed by a return to near normal levels in a few days; (2) increase of tissue capillarity; (3) increase of the red cell concentration of 2,3-diphosphoglycerate (DPG), a compound that decreases hemoglobin (Hb)-O_2 affinity thereby enhancing O_2 delivery to tissue. At *hemopoietic level*, hypoxia stimulates spleen and bone marrow leading to: (1) progressive increase of circulating hemoglobin over a period of several months (but the advantage of increased blood O_2 capacity are set off by increased blood viscosity); (2) faster replacement of relatively "old" red blood cells by "young", fresh red blood cells with more favorable O_2 transport characteristics. At *metabolic level*, although mitochondria and cellular oxidative machinery are slightly more plentiful in some animals native to altitude than in sea level controls, the importance of this adjustment in humans is questionable and general consensus is now against this possibility [9].

Literature

The purpose of this brief review is to analyze the mechanisms underlying the response of the gas transport system to hypoxia in resting subjects. Figure 1 shows a summary of available literature [8,10-21]. Unless otherwise stated, the figure reports blood gas transport data relative to Caucasian subjects exposed to real or simulated altitudes >4300m, along with additional data referring to natives to the same or lower altitude, as well as subjects with altitude-related disorders. The relevant data dispersion is caused by the combination of the following features: (1) Difficult operating conditions in several studies performed at altitude; (2) Different duration times of altitude exposure of the subjects prior to analyses, from a few hours to several days or weeks; and (3) unaccuracies in defining either altitude or barometric pressure. Actually, the equation proposed by the International Civil Aviation Organization to derive the barometric pressure from altitude:

$$P = P_0 e^{-Mgh} / RT$$

where P_0 is pressure at sea level, M is the average molecular weight of gas molecules, g the acceleration of gravity, and h the height, provides a low guess of the real barometric pressure. On the summit of Mt.Everest, this discrepancy accounts for up to 7% [22], which has enormous implications for gas transport [23].

Despite data dispersion, decreasing trends are uniformly observed for arterial O_2 tension (P_aO_2), arterial O_2 saturation (S_aO_2) and P_aCO_2, whilst pH_a and the blood molar ratio [DPG]/[Hb] increase with altitude. In general, data taken under simulated altitude conditions in hypobaric chambers [14,15] are within the limits of those taken under real altitude conditions, with the exception of P_aO_2 and DPG. Blood [Hb] always increases, a common finding in all studies, but since it depends on both degree and duration of hypoxia, this variable can not be conveniently plotted as a function of altitude. Indeed, serum erhytropoietin peaks a few days after hypoxic exposure followed by progressive

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which half of hemoglobin is saturated with O_2; S_aO_2, arterial O_2 saturation; $\Delta O_{2(a-v)}$, arterial-to-venous O_2 gradient.

decrease during the following weeks, leading to maintained or slightly decreasing blood [Hb] [24]. In addition, occurrence of striking differences among various populations living at high altitudes also suggests presence of genetic-related patterns [25].

In this discussion, it is convenient to set an arbitrary altitude of ~4300m, roughly corresponding to a reduction of inspired PO_2 by one-half. Indeed, this altitude is near the highest altitude to which man can be acclimatized and can live and perform work for months [6]. Severe hypoxic stress prevents establishment of permanent human settlings above 4500m, and induces >50% incidence of acute altitude-related disorders in sojourners and trekkers [26]. Although it is questionable whether the process of human adaptation to hypoxia would never be considered accomplished [8], it is also useful to compare groups of subjects characterized by different degrees of adaptation. Indeed, compensatory mechanisms may exist in individuals acclimatized to lower altitudes that induce different responses during adaptation to higher altitudes. Whilst ~1% of world population reside at altitudes exceeding 3300m [27], only two populations permanently reside at altitudes up to 4300-4500m. Himalayan Sherpas are known as healthy, well-adapted, virtually immune from altitude-related disorders [28]. In contrast, Andean Quechuas apparently did not develop adaptation as shown from their higher erythropoietic stimulus [29]. Finally, subjects suffering from acute mountain sickness (AMS) [30] represent the case of failed acclimatization process. This failure helps to understand the gas transport system at altitude as it does not involve other possibly implicated systems as blood rheology and hence microcirculation [31].

Blood gases and acid-base balance

The P_aO_2 value progressively decreases with altitude. Whilst P_aO_2 in AMS subjects was always lower than that of matched controls [16,18,21], the effects of acclimatization on P_aO_2 are not clear. In one study, 18 days acclimatization to 4300m increased P_aO_2 [17]. Also, if American Indians are to be considered poorly adapted to hypoxia, then their lower P_aO_2 with respect to Caucasians is not surprising [10]. However, another study failed to observe any effect of 3 weeks adaptation to 5050m nor differences in P_aO_2 of Sherpas and Caucasians acutely exposed to 6450m [21]. The ventilatory determinants of P_aO_2, i.e., the gas exchange ratio and alveolar ventilation, are outside the limits of this review, but, as originally pointed out, an adaptive reduction of alveolar-arterial O_2 gradient in the course of acclimatization would represent an effective defense against hypoxia [6]. Thus, the classical, now 25-years old hypothesis, that incomplete red cell equilibration along the pulmonary capillary is crucial to determine P_aO_2, appears still fully valid [32].

Graphical representation of the CO_2 hydration reaction ($H_2O+CO_2<=>H^++HCO_3^-$) by the pH-HCO_3^- diagram (Figure 2) shows that both volatile (CO_2) and metabolic (H^+) factors determine blood pH. The changes of the former follow the buffer lines, whilst changes of the latter follow the iso-PCO_2 curves. The base excess (BE, i.e., the amount of fixed H^+ that would have to be added to blood to titrate it to pH 7.4 at a PCO_2 of 40 mmHg at 37°C [33]) helps to assess the contribution of metabolic H^+ to acid-base imbalance: in the -2 to +2 mEq/l range, altered PCO_2 is the only contributor to acid-base imbalance; otherwise, metabolic H^+ is involved. In healthy humans, pH_a is allowed to fluctuate within a rather narrow range (7.35-7.45). The control systems that titrate pH_a to its normal value (7.40±0.02) are: (1) Body fluids buffer systems, which operate within

fractions of second after the onset of the stimuli; (2) Ventilatory response (fast, but with 50-75% effectiveness); and (3) Metabolic compensation (slow, but powerful).

In humans exposed to hypoxia, the decrease of alveolar PO_2 is accompanied by decreasing alveolar PCO_2 [34]. The hypothetical case of acute exposure to approximately 5000m is represented in the pH-HCO_3^- diagram by moving from 1 to 2 along the buffer line at BE=0 mEq/l. The effect of [Hb] on the slope of the buffer line is here neglected. The resulting alkalinization triggers responses aimed at titrating blood pH back to 7.4, but since the kidney is not able to fully accomplish this task at altitude, blood remains alkaline (3 in the diagram). Perhaps this is due to the slowness of renal compensation that can't cope with continuous CO_2 washout from the lungs, but the reasons for this lack of compliance are not yet understood. Actually, at 6300-6450m, when considering the increase of [Hb], BE was -6 mEq/l, whereas a BE of -10 to -9 mEq/l would have been necessary for complete metabolic compensation [13,21].

Comparative analysis of the pH-PCO_2 relationships in other groups of subjects helps to assess the above issues. In Sherpas, P_aCO_2 is higher, and their pH_a is lower than in Caucasians [21]. As BE is comparable in the two groups, one can infer that less hypoxic ventilatory drive in Sherpas [35] prevents excessive fall of P_aCO_2 and rise of alkalosis. Probably, low DPG in Sherpas' blood contributes to keep high S_aO_2 to a larger extent than hyperventilation does in Caucasians. On the other hand, the high pH_a value estimated on a Mt.Everest summiter [13] is probably the consequence of extreme hyperventilation that could have been beneficial for blood O_2 loading. Indeed, this subject had an extremely powerful ventilatory drive due to exercise and the need to take off his oxygen mask 10 minutes before sampling [36]. Note also the steepness of the pH-PCO_2 relationship at low PCO_2 values, which causes powerful increases of alkalosis, particularly so under hypocapnic conditions [37]. At lower altitudes, subjects who are characterized by altitude-related conditions also develop high pH_a, likely secondary to extreme hyperventilation and nearly uncompensated respiratory alkalosis.

The oxygen equilibrium curve

The main factors that influence the Hb-O_2 equilibrium curve (OEC) are pH, PCO_2 and the [DPG]/[Hb] ratio. Here, Hb fenotype, temperature, and the level of carbonmonoxy-Hb are irrelevant. Several studies in the past have already addressed the question on how altitude alters OEC and hence P_{50}, i.e., the PO_2 at which Hb saturation for O_2 is 50% [5,6].

Red cell DPG is critical during hypoxia. A glycolytic intermediate occurring in all tissues, only in the red cell DPG reachs sizeable concentrations. Hypoxia further increases DPG by three mechanisms: (1) Preferential DPG binding to deoxygenated Hb [38] and high levels of this Hb during hypoxia decrease free DPG levels thereby enhancing synthesis [39]; (2) Alkalosis associated with hypoxia stimulates DPG mutase and inhibits DPG-phosphatase [39]; (3) Hemopoietic stimulation increases the fraction of "young", DPG-rich red cells [19,24]. As a result of these synergisms, the [DPG]/[Hb] ratio always increases with hypoxia, but Figure 1 shows that the dispersion of DPG data is much higher than that observed for the other parameters. Possibly, the above mentioned variability factors are complicated by additional problems as the time duration of hypoxia, the degree of effort over the days or weeks before sampling, and technical difficulties related to blood storage, extraction and enzymatic analysis with

spectrophotometric methods. Indeed, since DPG is a rather unstable metabolite, the blood sample should be obtained in suitable anticoagulant, and stored for no more than a few hours at ice temperature before enzymatic analysis.

Increased DPG shifts the OEC to the right in antagonism with alkalosis. An algorithm [40] allows to assess the effects of those factors on the OEC even under the extreme conditions of pH, PCO_2 and [DPG]/[Hb] found at high altitude: the discrepancy between measured P_{50} and that calculated from the algorithm accounts for 0.2-0.4 mmHg [13]. In Caucasians at 6300m, the P_{50} value is higher than at sea level (29.8±2.2 mmHg [13] *vs* 27.5 mmHg [41]). Thus, the rightward shift caused by DPG appears stronger than the leftward displacement caused by alkalosis. As a matter of fact, an increase of the [DPG]/[Hb] molar ratio from 0.80 (sea level) to 1.36 (6450m [21]) would have required an increase of pH_a from 7.40 to 7.56 for complete compensation, i.e., much stronger alkalosis than actually measured. On the other hand, should alkalosis be fully compensated by metabolic acidosis, thus offsetting the effect of pH, then P_{50} would have been 33 mmHg.

There are very few data on DPG in altitude natives dwelling at altitudes >4300m, and apparently no data at all for subjects with altitude-related disorders. However, in Sherpas, the [DPG]/[Hb] ratio should be less than in Caucasians. Although at 3800m the [DPG]/[Hb] ratio was the same in the two groups [29,42], at 5050m it was definitely lower in Sherpas than in Caucasians (1.04±0.04 *vs* 1.28±0.05, respectively [24]). It is likely that such trend does continue even at higher altitudes. In addition, when the [DPG]/[Hb] ratio is calculated by the algorithm from actual Sherpas P_aO_2, P_aCO_2, pH_a and S_aO_2, it is estimated at ~1.2 [21].

Tuning of blood O_2 transport

Blood OEC shifts are important to optimize the blood-O_2 transport. The physiological relevance of the OEC sigmoid shape is to maintain high arterial-to-venous O_2 gradient ($\Delta O_{2(a-v)}$) at high venous PO_2 (P_vO_2). High $\Delta O_{2(a-v)}$ is favourable as, at the same work load, it either decreases cardiac work or increases the O_2 transport [43]. At sea level, assuming constant P_aO_2 and P_vO_2 levels, rightward shifts of the OEC increase $\Delta O_{2(a-v)}$ (Figure 3a) because the *venous* point is located on the steep portion of the OEC. Therefore, small P_{50} increases reflect into considerable increases of $\Delta O_{2(a-v)}$. Although this situation apparently holds for moderate hypoxia (Figure 3b), it is reversed under severe hypoxia conditions, where the *arterial* point lies in the steep portion of the OEC (Figure 3c). Under this condition, the same P_{50} increase as in Figure 3a reflects in considerable *decrease* of $\Delta O_{2(a-v)}$. In theory, the threshold altitude above which a rightward shift of the OEC should be regarded as a maladaptive response is near 5400m [44]. Thus, respiratory alkalosis is favorable at extreme altitude: at 6450m, alkalosis increases S_aO_2 by at least 5% with respect to an hypothetical non-alkalotic condition [21]. At 8848m, the extreme alkalosis inferred in a Mt.Everest summiter should have allowed this subject to maintain essentially same S_aO_2 as that measured at a much lower (2500m) altitude [13]. It is therefore evident how the mechanism triggered by alkalosis maintains $\Delta O_{2(a-v)}$ despite low P_aO_2, thereby implying greater efficiency and lower load to the circulation. Interestingly, theoretical considerations based on quite different principles, i.e., diffusion limitations at the alveolar-capillary interface, point to the same conclusion: right shifts of the OEC are favourable at sea level or moderate hypoxia, but not so at very high altitude [45].

Prolonged alkalosis, however, is not compatible with normal body function as it is widely known to impair the central nervous system. Indeed, there appears to be a trend towards less alkalosis with acclimatization: acclimatized subjects develop less alkalosis at the same altitude, and AMS subjects are frankly alkalotic. Although it is not clear whether altitude-related disorders stem from alkalosis or if the reverse is true, alkalosis remains sustained even in subjects who do not experience AMS symptoms, but the reasons for which alkalosis is deleterious at sea level, but is relatively well tolerated at extreme altitude, are unknown. As a matter of fact, the most important action of a drug used to fight the effect of AMS, i.e., acetozolamide, is to lower pH_a by inhibiting the enzyme carbonic anhydrase [27].

Conclusion

Analysis of the response of the blood-gas transport system to hypoxia indicates that, in resting subjects, the need to oxygenate tissues conflicts with the need to maintain H^+ homeostasis. In other words, at high altitude the cost of meeting tissue requirements for O_2 is competitive with other body functions, that may become progressively impaired by alkalosis. The final situation represents a compromise between the respiratory stimulus, which is aimed at increasing blood alkalosis in order to optimize the O_2 tranport system, and the metabolic adjustment, which is aimed at re-establishing normal blood pH. Factors like the [DPG]/[Hb] ratio influence that balance by affecting S_aO_2 through mechanisms independent of respiration. Although metabolic and ventilatory responses to exercise in moderate hypoxia are not subjected to genetic influences [46], their role in determining the responses of the gas transport system to extreme hypoxia is still to be evaluated.

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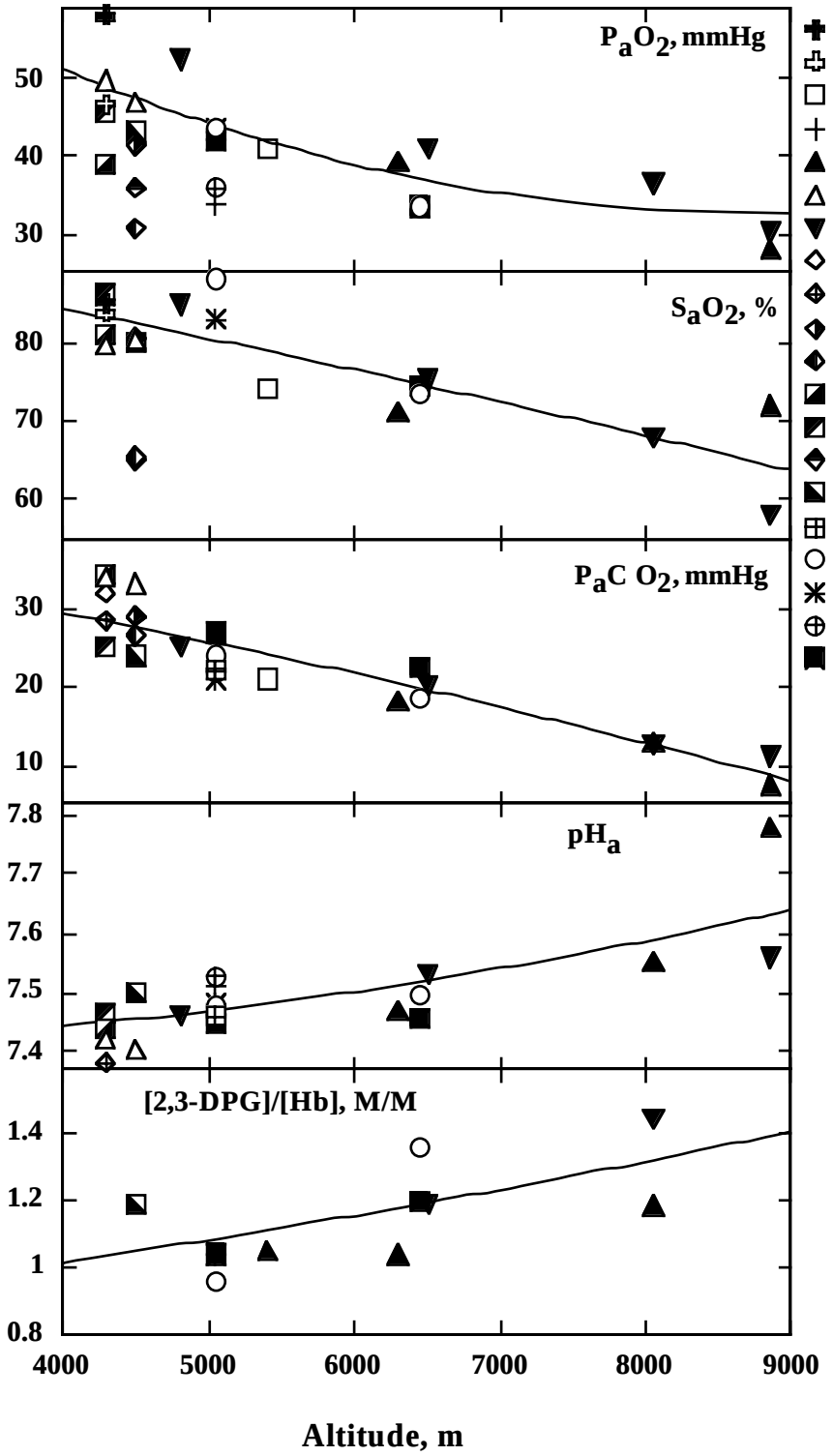
Legends to figures

Figure 1. Literature data of gas transport parameters at altitude >4300m in resting subjects. Unless otherwise stated, data refer to Caucasian subjects exposed to altitude. The curves represent the best fit obtained using only these data. SD bars are omitted for clarity.

Figure 2. pH-bicarbonate diagram representing the situation at sea level (1), after the respiratory response to acute exposure to approximately 5000m (2), and after partial metabolic readjustment (3). The long-dashed lines represent the buffer lines at [Hb]=15 g/dl.

Figure 3. Effects of a rightward shift of the O_2 equilibrium curve (~6 mmHg P_{50}, corresponding to an increase of the [DPG]/[Hb] ratio by 0.2 mole/mole) on the arterial-to-venous O_2 difference (ΔO_2). At sea level (3*a*) and at moderate hypoxia (3*b*), the shift increases ΔO_2, whilst this trend is reversed during severe hypoxia (3*c*). Further explanations in the text.



Barcroft 1923
Peruvians
Cerretelli 1976
Birmingham 1981
Winslow 1984
Winslow 1987 Peruvians
Sutton 1988 Simulated
Maclellan 1988 Simulated
Acetozolamide
Oelz 1989
AMS
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after 18 days
Bartsch 1990 AMS
Mairbaurl 1990
Kayser 1993
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AMS
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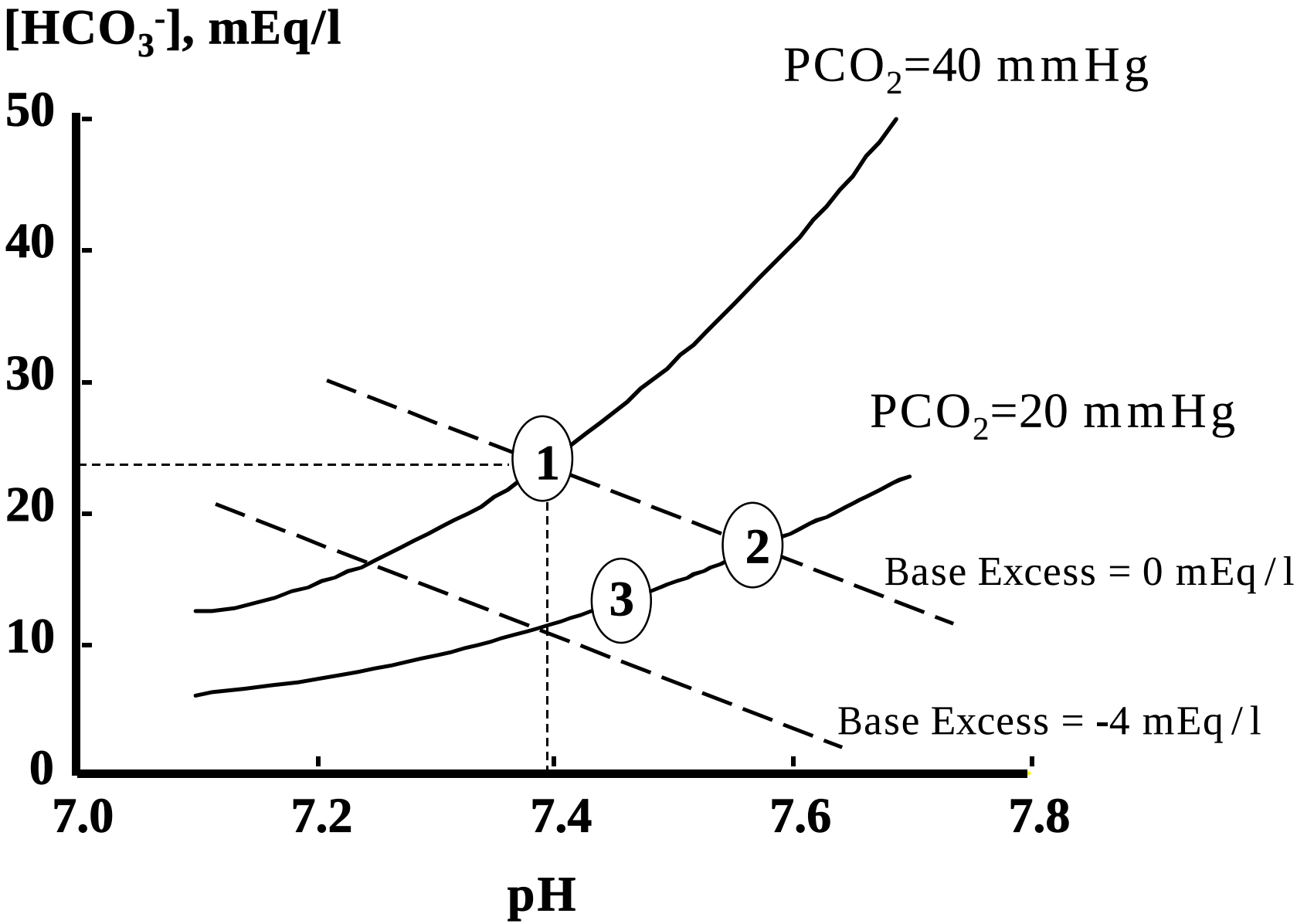
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PCO2=40 mmHg
PCO2=20 mmHg
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Base Excess = -4 mEq/l
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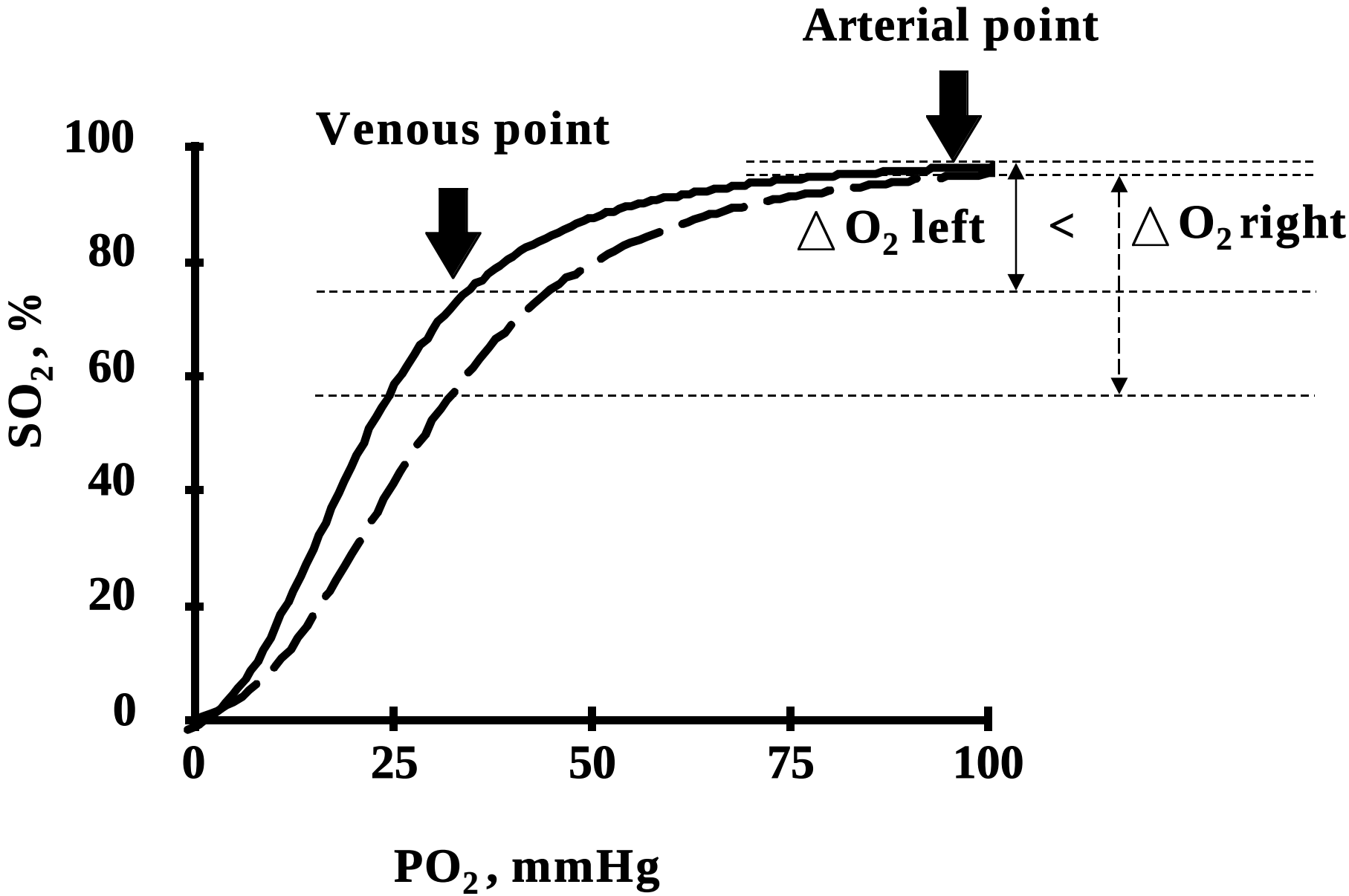
Sea level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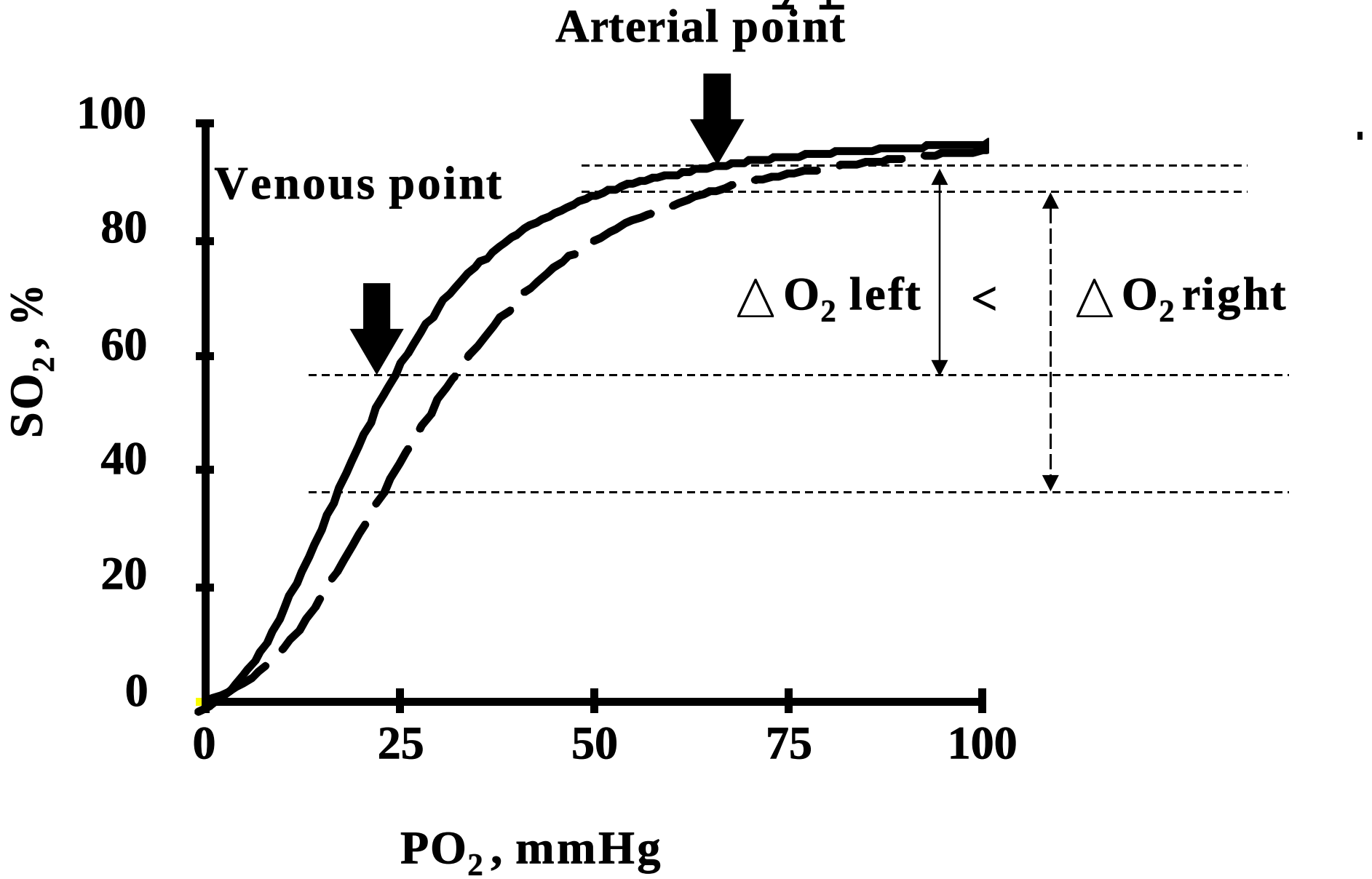
Moderate hypoxia



Severe hypoxia