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Medicine

The physiology of high altitude: an introduction to the cardio-respiratory changes occurring on ascent to altitude

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Both the high altitude physiologist and the intensivist are challenged by the human organism in a hypoxic environment. The variation in barometric pressure which occurs with latitude influences enormously the inspired oxygen concentration at extreme altitudes and can significantly effect performance. The cardio-respiratory changes which take place at high altitude, and in particular the putative control mechanisms increasing ventilation; changes in the oxygen-haemoglobin dissociation curve; diffusion limitation during exercise; cardiac function; the pulmonary circulation; and changes in erythropoiesis and fluid homeostasis are reviewed. © 2000 Harcourt Publishers Ltd

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Introduction

Both the high altitude physiologist and the intensivist are challenged by the human organism in a hypoxic environment and the true research potentials presented by high altitude, where the body is subjected to an essentially isolated hypoxic challenge, are only just beginning to be realised. This article will concentrate on those changes in cardio-respiratory physiology occurring in sea level dwellers on ascent to high altitude and which are perhaps of most interest to the anaesthetist or intensivist. The history of high altitude research is a fascinating adventure story which has been extensively reviewed in a recent book.[1]

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One of the problems when talking about high altitude is the absence of any universally accepted definition as to what exactly constitutes ‘high’. In this article ‘high altitude’ will be used for altitudes above 3000 m, above which most individuals will demonstrate marked physiological changes. The term ‘extreme altitude’, will be reserved for those altitudes above 6000 m, where permanent habitation is impossible and where any period of time spent there results in physical deterioration.

The Atmosphere

The position of the Earth in relation to the Sun and the Earth’s mass, which dictates it’s gravitational force, have combined to produce the conditions necessary for an oxidative atmosphere, unique within the solar system. A stronger gravitational force (as seen on the larger planets as Saturn and Jupiter) would retain all gases including hydrogen and helium, resulting in a reducing atmos-

phere. The weaker gravitational force of the smaller planets such as Mercury and the Earth's moon are unable to retain any form of atmosphere.

The surface temperature of the planet is determined largely by its distance from the sun. Using this fact to estimate the surface temperature of the Earth gives a result of –18°C. That the actual surface temperature is higher is due to the greenhouse effect. Incoming short-wave solar radiation passes easily through the earth's atmosphere and is absorbed by the earth, increasing its temperature and causing it to radiate infra-red (the wavelength of emitted radiation being inversely proportional to the temperature of a body). Rather than passing out of the atmosphere, this infra-red radiation is absorbed by atmospheric gases and then re-emitted, predominantly back towards the earth's surface, resulting in its heating. Water vapour is quantitatively the most important greenhouse gas present in the earth's atmosphere, although other gases, such as CO_2, have a more powerful effect per molecule.

The atmosphere is divided into a number of levels surrounding the Earth: the troposphere, the lowest part of the atmosphere, and the part responsible for most of the weather; the tropopause, the junction between the troposphere and stratosphere; the stratosphere, which extends to an average height of 50 km; and the stratopause, the junction between the stratosphere and the next layer of the atmosphere, the mesophere. The mesophere and other outer layers of the atmosphere will not be considered further here.

Within the troposphere heat is lost with increasing altitude. The fall in temperature with altitude, or lapse rate, is highly variable and influenced by latitude as well as a number of complex heat exchange processes occurring within the troposphere. An average lapse rate for temperate regions would be of the order of –6.5°C Km^{-1} resulting in a temperature around –60°C at the tropopause.

The tropopause is the point at which the atmospheric temperature gradient reverses and temperature increases with altitude. The temperature structure of the stratosphere effectively seals the troposphere preventing the escape of water from the lower atmosphere and maintaining a constant atmospheric composition. The stratosphere is exposed to ultra violet and other forms of ionizing radiation, and as a result of this a number of unique chemical reactions take place resulting in the production of gases such as ozone. The creation and destruction of ozone results in the strong absorption of ultra-violet radiation, which has the effect of warming the stratosphere, the temperature reaching 0°C at the stratopause.

Variations in barometric pressure with latitude and season

The troposphere extends to a height of approximately 7 km at the poles and 17 km near the equator. This difference in height is mainly due to a temperature effect. Tropical air is warmer than polar air and the expansion of tropical air transports more air to higher altitudes elevating the pressure there. This results in a significant increase in barometric pressure for a given altitude near the equator compared with at the poles. The barometric pressure at high altitude also changes during the year. Figure 1 illustrates the change in barometric pressure at 8848 m (the height of Mount Everest) with latitude during the summer, autumn and winter. These differences are of immense importance. Were Mount Everest in Alaska at a latitude of around 60° N it would be almost certainly impossible to climb it without supplementary oxygen, the difference in barometric pressure at 8848 m between these two latitudes being of the order of 3.5 kPa (26 mm Hg) during the autumn climbing season.[2] The winter decrease in barometric pressure is an additional difficulty to those attempting to make winter ascents of Mount Everest. To the author's knowledge only one such ascent has been made without supplementary oxygen, by the Sherpa Ang Rita in December 1987.

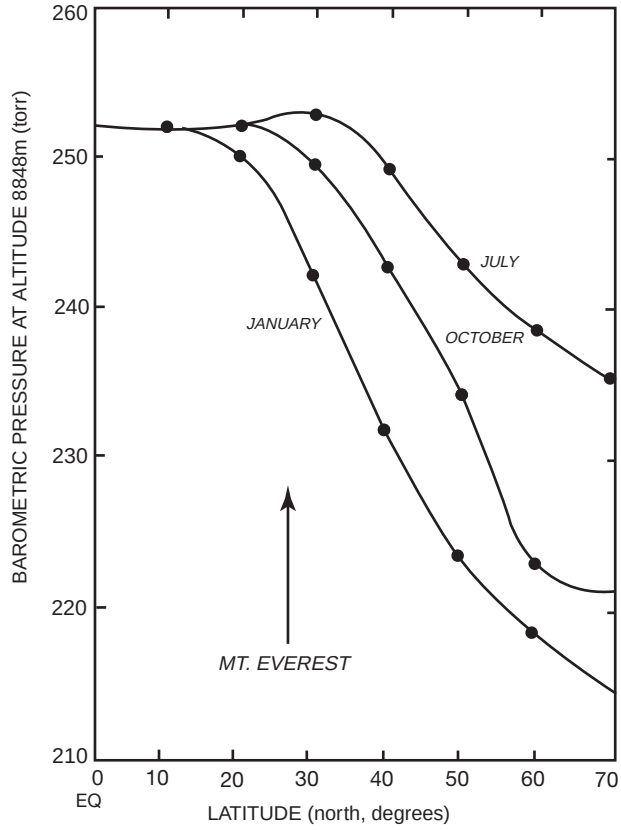

Fig. 1 Barometric pressure at altitude of Mount Everest plotted vs. latitude in Northern Hemisphere for midsummer, midwinter and October (the preferred month for climbing in the post-monsoon period). From West JB, Lahiri S, Maret KH, Peters RM Jr, Pizzo CJ. Barometric pressures at extreme altitudes on Mt. Everest. J Appl Physiol 1983; 54: 1188–1194.[2]

Respiratory acclimatization

Figure 2 illustrates the oxygen cascade at sea level and at 5800 m (where the barometric pressure is around one-half of the sea level value) both at rest and during maximal exercise. The slopes of the altitude curves are less steep than the sea level curves and one can consider the adaptive processes of acclimatization as working to

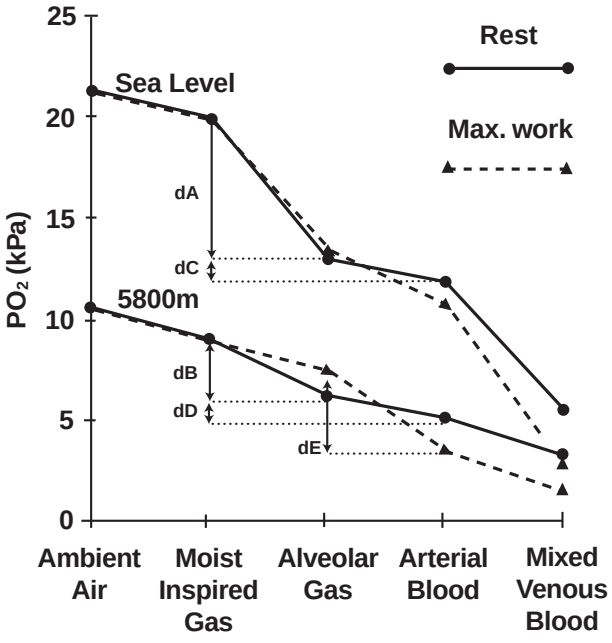

Fig. 2 Oxygen cascade at sea level and at 5800m during rest and exercise. Adapted from Pugh LGCE The Scientific Basis of Medicine Annual Reviews, 'Man at high altitude.' 1964; p 32–54.

reduce, as much as possible, the size of each step in the cascade between ambient air and mixed venous blood (representative of tissue oxygenation) resulting in a final partial pressure at high altitude that is not greatly different from the sea level value.

Influence of water vapour on inspired oxygen tension

Inspired air is warmed and saturated with water vapour in the upper airways. The inspired O_2 tension (PiO_2) is given by the equation:

$$PiO_2 = 0.2094\ (P_B – 6.3)$$

where 0.2094 is the atmospheric concentration of oxygen; P_B the barometric pressure, and 6.3 the water vapour pressure at body temperature, 37°C, in kPa (or 47 if using mm Hg). Thus, the effect of water vapour pressure becomes increasingly important with increasing altitude being only around 6% of the total barometric pressure at sea level, but almost 19% at the summit of Mount Everest where the barometric pressure is around 33.3 kPa (250 mm Hg) resulting in a considerable reduction in PO_2 between ambient and moist inspired air.

Hypoxic and hypercapnic ventilatory responses

Exposure to even mild hypoxia stimulates the peripheral chemoreceptors as witnessed by the increase in activity in the carotid sinus nerve. However, there is no increase in ventilation up to an altitude of around 3000 m[3], corresponding to an inspired PO_2 of 13.3 kPa (100 mm Hg) and equivalent to an arterial PO_2 of around 6.7 kPa (50 mm Hg) (Fig. 3a). This lack of response is puzzling,

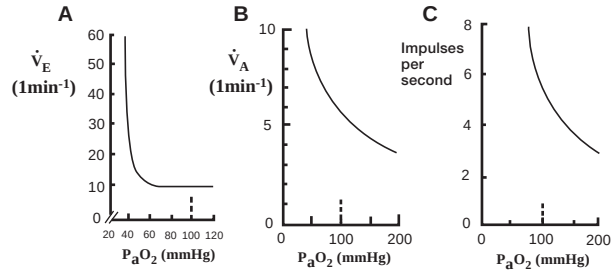

Fig. 3 The ventilatory response to hypoxia. A, shows the acute response before acclimatization. B, shows the response after acclimatization and C, the peripheral arterial chemoreceptor response (sinus nerve discharge). From Wolff CB, The control of ventilation in hypoxia, I. International Society of Mountain Medicine Newsletter, 1998; 8(1): 3–6.

but it is thought that up to 3000 m the hypoxia stimulated increase in cerebral blood flow (CBF) which occurs at altitude[4] decreases the cerebral extracellular PCO_2, which, in turn, increases the pH around the central medullary chemoreceptors causing them to exert an equal and opposite inhibitory effect opposing any increase in ventilation. With increasing acute hypoxia peripheral chemoreceptor stimulation exceeds the central inhibition and ventilation increases.

The increase in alveolar ventilation, which now occurs decreases $PACO_2$ and $PaCO_2$, further increasing the pH of cerebral extracellular fluid (ECF). This would act as a brake to respiration were it not for the changes which take place in the hypercapnic ventilatory response (HCVR). Figure 4 illustrates the effect of acclimatization on the HCVR at an altitude of 4340 m. After 20 days at altitude, sea level values of $PACO_2$ produce a massive increase in ventilation. The most likely explanation of these changes is that some form of adjustment of the pH of the cerebral ECF takes place, but the mechanism is unclear. At moderate altitudes it may simply be the return towards normal of the increased CBF, which occurs over 3 or 4 days returning the pH towards normal, but this is not sufficient to explain the mechanism at higher altitudes. Renal excretion of bicarbonate bringing about passive changes in CSF pH, although perhaps having a contributory role,

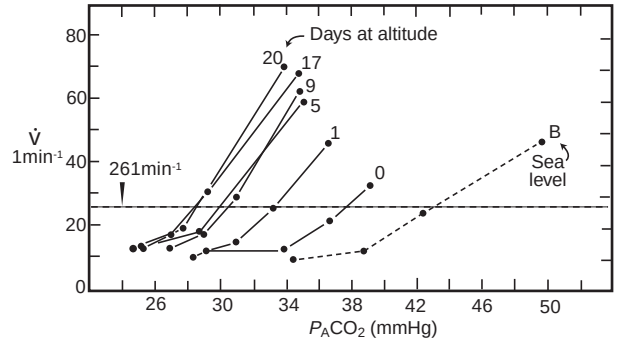

Fig. 4 Effect of acclimatization on the hypercapnic ventilatory response at 4340 m. From Kellog RH. The rôle of CO_2 in altitude acclimatization. In: Cunningham DJC, Lloyd BB (eds) The Regulation of Human Respiration. Oxford: Blackwell Scientific, 1963, 379–394.

is too slow and too incomplete to account of the necessary change in pH. This leaves some form of central mechanism to adjust CSF pH, but, contrary to popular belief, it seems unlikely that this is due to the active transport of bicarbonate.[5] The generation of lactic acid, which would buffer the increased pH, has been put forward as another possible mechanism, but evidence is lacking. The end result of these changes is that the hypoxic ventilatory response (HVR) is significantly increased in the acclimatized individual and the ventilatory response to hypoxia is directly related to the rate of peripheral chemoreceptor discharge (compare Fig. 3b & c). The use of carbonic anhydrase inhibitors to aid acclimatization will be discussed in the next article.

The increase in ventilation occurring at high altitude is of crucial importance to defend alveolar PO_2. Despite the fact that in 1924 E.F. Norton reached 8500 m on the north side of Everest without supplementary oxygen, it was not until 1978 that Rheinold Messner and Peter Haebler made the first successful 'oxygenless' ascent. Indeed, until their ascent it was widely believed in the physiological community that such a feat was impossible. In the early 1900s, the success of the Duke of Abruzzi's Italian expedition in reaching 7500 m on K2 led notable physiologists of the day, including Douglas and Haldane, to declare that the lung must actively secrete oxygen.[1] In 1981, the American Medical Research Expedition to Everest (AMREE) succeeded in sampling alveolar gas on the summit of Mount Everest,[6] and in 1985 a low-pressure chamber study, Operation Everest 2, further elucidated the mechanisms of survival at extreme altitude.[7] The picture that emerged was of a very high level of hyperventilation with an alveolar PCO_2 on the summit of Everest of around 1 kPa (7.5 mm Hg) corresponding to an increase in ventilation of five to six times the resting sea level value. These results have recently been confirmed by work from the British 40th Anniversary Mount Everest Expedition.[8] Figure 5 is an O_2–CO_2 diagram which combines the pioneering work of Rahn and Otis[3] with the results from AMREE. Note that once a PAO_2 of around 35 mm Hg (4.7 kPa) is reached the value does not fall any further despite increasing altitude as one moves left and down along the curve. Increasing hyperventilation serves to reduce $PACO_2$ and in so doing maintain PAO_2. The effect of hyperventilation can also be clearly seen in Figure 2. The fall in PO_2 between inspired gas and alveolar gas at 5800 m (dB) is only one-half of its sea level value (dA) as a result of a doubling in ventilation. Note also that during maximal exercise at altitude there is a further increase in PAO_2 owing to the accompanying increase in ventilation.

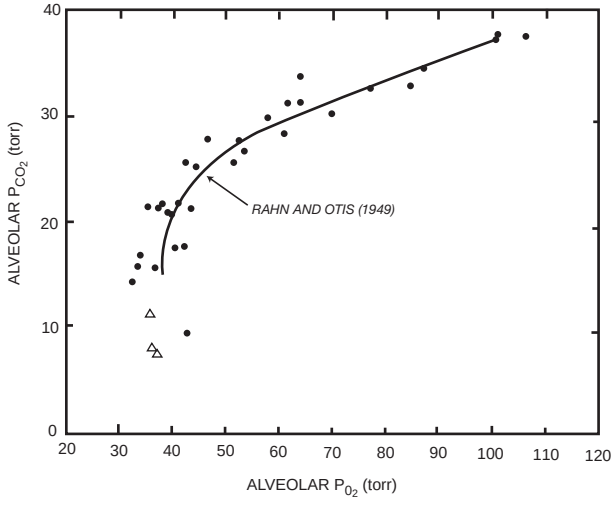

Fig. 5 O_2–CO_2 diagram showing alveolar gas composition in acclimatized subjects as altitude is increased (moving from top right to bottom left). From West JB, Hackett PH, Maret KH et al. Pulmonary gas exchange on the summit of Mount Everest. J Appl Physiol 1983; 55: 678–687.[6]

Following on from this it would seem logical that the greater the response to hypoxia the better a subject will perform at altitude. This is not necessarily the case. High altitude natives who traditionally perform well at altitude have a relatively blunted HVR,[9, 10] and in a study of six elite high-altitude climbers, including the first three Western climbers to reach the summit of Everest without supplementary oxygen, their HVR was found to be no different from a control group.[11] While there is some evidence that a high HVR may confer some degree of protection against acute mountain sickness,[12] it also predisposes to periodic breathing during sleep resulting in episodes of marked desaturation.[13]

Oxygen–haemoglobin dissociation curve

A further effect of hyperventilation and the resultant respiratory alkalosis is seen on the oxygen-haemoglobin dissociation curve. Although metabolic compensation by the renal excretion of bicarbonate ions returns the pH towards normal, even after several weeks it rarely falls to its sea-level value. The author's arterial blood gases after 2 months at Everest base camp, at an altitude of 5300 m, are shown in Table 1. The ongoing respiratory alkalosis stimulates the production of 2,3-diphosphoglycerate (2,3-DPG) shifting the oxygen–haemoglobin dissociation curve to the right. At extreme altitude, however, the profound respiratory alkalosis resulting from the massive increase in minute volume required to defend alveolar PO_2 offsets any effect of 2,3-DPG, and the oxygen–haemoglobin dissociation curve is shifted to the left. An estimate of the P_{50} on the summit of Mount Everest during the AMREE gave a value as low as 2.5 kPa (19 mm Hg, normal value: 3.5 kPa, 26.5 mm Hg).[6] The effect of this is to increase the oxygen affinity of haemoglobin and, thus, increase oxygen uptake in the alveolar capillaries.

Table 1 Arterial blood gas results after 2 months at 5300 m

pH	7.450
pCO_2	2.83 kPa
pO_2	6.63 kPa
O_2 saturation	87.9%
standard bicarbonate	18.3 mmol / l
base excess	–7.4 mmol / 1

Diffusion limitation at altitude

Fick's law of diffusion describes the factors governing the transfer of a gas across a tissue:

$$V = A/T\ D\ (P_1–P_2)$$

where V is the flow of gas across the tissue; A is area; T is thickness; D is a diffusion constant for the gas proportional to the solubility of the gas and inversely proportional to its molecular weight; and $P_1–P_2$ is the difference in partial pressures across the tissue. Except in the case of high-altitude pulmonary oedema, which will be discussed in the next article, the only difference between altitude and sea level is a reduction in the partial pressure gradient for oxygen across the alveolar-capillary membrane. Despite this, while resting at high altitude the alveolar-arterial difference of oxygen ($A\text{-}aO_2$) is not greatly different from the sea-level value, (compare dC and dD in Fig. 3). With exercise, however, the difference is greatly increased (compare dD and dE in Fig. 3) as a result of diffusion limitation. This effect is particularly pronounced at extreme altitude where, even at rest, marked diffusion limitation occurs because of the feeble PO_2 gradient across the alveolar-capillary membrane, which does not permit equilibration of the PO_2 between the alveolar gas and end-capillary blood in the time that it takes for a red cell to traverse the alveolar capillary.[6]

Cardiovascular changes at altitude

It is impossible to separate the cardiovascular and respiratory systems when considering oxygen delivery to the tissues. Acute exposure to high altitude results in an increase in heart rate and cardiac output both at rest and for a given level of exercise compared with at sea level. With acclimatization resting heart rate returns towards its sea level value up to an altitude of around 4500 m, but for a given level of exercise it remains higher. Maximum heart rate, however, is less than at sea level, although the maximum exercise level is also reduced.[14] The reason for this reduction in maximum heart rate is controversial. Cardiac β-receptors undergo down regulation at altitude and it has been speculated than this functions as a protective mechanism against ischaemia. However, as heart rate is higher for any given level of exercise, it is perhaps more likely that the reduction in maximum heart rate simply reflects the reduction in the maximum exercise level which occurs at high altitude.

Despite the increase in heart rate for a given level of exercise, the cardiac output response in acclimatized subjects remains unchanged. As heart rate is increased, this implies that stroke volume must be reduced. Right heart studies during Operation Everest 2 demonstrated that right atrial pressure fell with altitude despite an increase in pulmonary artery pressure. Pulmonary capillary wedge pressure at rest did not change from sea level, but was reduced with exercise. The relationship between right atrial pressure and stroke volume was well preserved. In addition, breathing supplementary oxygen did not improve stroke volume for a given filling pressure.[14] These results were corroborated by echocardiographic studies. Taken together these findings suggest that myocardial contractility is well preserved in hypobaric hypoxia and, indeed, in general, the normal heart tolerates even severe hypobaric hypoxia exceedingly well. Cardiac arrhythmias are exceedingly rare at high altitude and even at extreme altitude the ECG shows only the changes of pulmonary hypertension.

Pulmonary circulation

Exposure to hypobaric hypoxia produces pulmonary vasoconstriction resulting in pulmonary hypertension proportional to the degree of hypoxia. The hypoxic pulmonary vasoconstriction (HPVC) is non-linear and highly variable between individuals. In normal lowland responders it commences at a PAO_2 of approximately 10 kPa,[15] which corresponds to an altitude of around 2000 m. The pulmonary pressor response is further enhanced with exercise, with the mean pulmonary artery pressure (PAP) rising as high as 55–60 mm Hg during exercise at extreme altitude.[16] During acute exposure to hypoxia breathing oxygen restores resting pulmonary artery pressure (PAP) to its sea level values, but once acclimatization has occurred this is no longer the case. This effect can be seen as early as 3 weeks after exposure to high altitude,[16] suggesting that even after this relatively short time period structural changes are occurring in the pulmonary arteries. The variation in hypoxic pulmonary vasoconstriction between individuals within a population and its possible role in the pathogenesis of high-altitude pulmonary oedema will be discussed in the next article.

Although the hypoxic pulmonary pressor response was first described in 1946,[17] it is only in recent years that it has become evident that the dynamic control of pulmonary vascular pressure is dependant on mediators released from the vascular endothelium, and, in particular, on the endothelial-derived relaxing factor, nitric oxide; the eicosanoids prostacyclin; and thromboxane, endothelin and atrial natriuretic peptide. The interplay of each of these factors in the control of the pulmonary circulation at altitude remains to be elucidated.

The response of the pulmonary vasculature to hypobaric hypoxia differs between visitors and residents at altitude. Natives in the Andes exhibit an increase in PAP with altitude (although the slope of the PAO_2–PAP curve is less steep than in lowland visitors), but native Tibetans appear to have little or no pulmonary pressor response to hypoxia either at rest or during exercise.[18] Five healthy 22-year-old males who had lived all of their lives at altitudes ≥ 3600 m were studied in Lhasa (altitude 3658 m) at rest and near maximal exercise. Mean PAP at rest was within normal limits when breathing ambient air (15 ± 1 mm Hg) and showed only a minimal increase when breathing a hypoxic gas mixture (FiO_2 0.14) or during near-maximal exercise.[19]

Likewise in a post-mortem study of native Ladakhi Himalayan Highlanders no medial hypertrophy of the pulmonary arteries or muscularization of the arterioles was found, which is in marked contrast to the hypertrophic changes found in the majority of South American high-altitude natives.[20] This would suggest that Himalayan highlanders, probably the world's longest high-altitude residents, exhibit a remarkable degree of adaptation in the pulmonary circulation, which may go some way to explaining their consistently good physical performance at high-altitude.

Cerebral circulation and cerebral function

As mentioned above, the effect of acute hypobaric hypoxia is to increase cerebral blood flow (CBF), but the increase is limited by the concomitant reduction in $PaCO_2$ occurring as a result of hyperventilation. Severinghaus, showed a 24% increase in CBF after 6 to 12 h of exposure to 3810 m, in comparison with the sea-level values, which had fallen to a 13% increase over sea level after 3–5 days.[4] Similar increases were found in carotid and vertebral artery flow at 4300 m, which had returned to sea-level values after 4–12 days.[21]

It is generally accepted that exposure to hypobaric hypoxia impairs cognitive function. As would be intuitively expected the degree of dysfunction is proportional to the altitude, but what is surprising is the low altitude at which changes can first be detected. Impairment of task learning can be demonstrated at an altitude of 2440 m (the cabin pressure of most commercial aircraft is maintained at a pressure equivalent to an altitude of between 2000 and 2500 m), although this only influences performance if the task is unfamiliar.[22] Acclimatization appears to give some degree of protection when compared with acute exposure; however, there is clear evidence of residual impairment of CNS function after exposure to high altitude which persists for up to at least 1 year after exposure.[23]

Fluid and electrolyte changes

The normal mechanisms of fluid homeostasis are perturbed at high altitude and the situation is further complicated by the effect of exercise. On exposure to altitudes of between 3500 and 4000 m, plasma volume is reduced by between 3 and 5 ml/kg. This occurs relatively rapidly after arrival at altitude and the deficit would appear to persist for at least 3 or 4 months before starting to return towards normal.[24] Total body water is reduced by around 5%.[25] The decrease in total body water is probably due to decreased water intake, possibly due to alterations in thirst regulation, coupled with increased insensible losses and an inappropriately unchanged urine output. Sodium and potassium balance seem to be unchanged.

Despite this reduction in body water and the resultant increase in osmolality, there is little evidence that hypoxia has any effect on anti-diuretic hormone secretion, except perhaps in some cases of acute mountain sickness.[26] The renin-angiotensin-aldosterone system, however, presents a more complex picture.[27] Both exercise and hypoxia stimulate renin release, but aldosterone release is decreased at high altitude. Despite a reduction in angiotensin converting enzyme (ACE) concentration, ACE activity does not appear to be affected by hypoxia. Aldosterone release in hypoxia is reduced in response to a number of different secretory stimuli suggesting that the mechanism is distal to any receptor or second messenger. In addition this is not a generalized sensitivity of the adrenal cortex to hypoxia, as cortisol release remains normal. Recent work in rats has shown that that relatively short-term hypoxia decreases expression of the gene for a late-pathway enzyme unique to aldosterone synthesis (P-450c11AS) leading to a decrease in aldosterone production.[28] In addition, atrial natriuretic peptide (ANP) concentration increases with hypoxia, albeit to a limited extent. It is not clear if the stimulus for this is hypoxia per se or the resulting increase in PAP, but ANP inhibits aldosterone release from the adrenal cortex.[29] Either or both of these mechanisms may be responsible for the seeming paradox between renin and aldosterone concentrations. With time at altitude, plasma volume tends towards normal, although it does not return to baseline values while the subject remains at altitude.[24]

Haematology

The rapid reduction in plasma volume on exposure to high altitude results in an increase in haemoglobin concentration. At the same time as the reduction in plasma volume, hypoxia stimulates renal and hepatic erythropoietin production stimulating erythropoiesis. The erythropoietin response is rapid, with increased concentrations being detectable only 2 h after arrival at altitude. The response peaks at around 2 days and, providing the subject remains at the same altitude, has returned to sea-level values after 3 weeks. Despite this return to sea-level concentrations, erythropoiesis continues at above base line levels.[30] Obviously if the subject ascends to a higher altitude the increased hypoxia will continue to trigger erythropoietin production. After around 6 weeks, despite a continuing increase in erythropoiesis and red-cell mass, haemoglobin concentration starts to plateau off because of the increase in plasma volume.[24] The increase in haemoglobin concentration has the effect of increasing the arterial oxygen content of the blood (CaO_2) for any given oxygen saturation. Thus, a well-acclimatized individual will have a similar CaO_2 and oxygen delivery (as cardiac output is unchanged) at altitudes of up to 5500 m as at sea level.

Peripheral tissue changes

Despite the importance of this final step in the delivery of oxygen to the mitochondria, relatively little is known about the adaptive changes which take place in the peripheral tissues at altitude. Capillary density in muscle is unchanged, although the average diameter of muscle fibres appears to be reduced. One possible advantage of this change would be to reduce the distance that oxygen

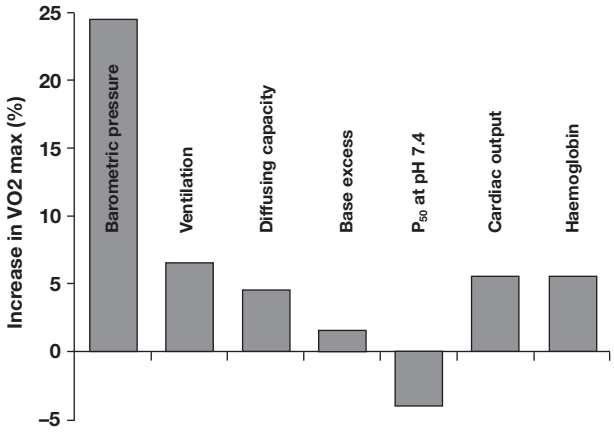

Fig. 6 Sensitivity of calculated VO_2 max on summit of Mount Everest to 5% changes in a number of factors determining O_2 delivery. From West JB. Climbing Mount Everest without supplementary oxygen: an analysis of maximal exercise during extreme hypoxia. Respir Physiol 1983; 52: 265–279.[35]

has to diffuse from the capillaries to the mitochondria. Muscle myoglobin appears to be increased at altitude improving oxygen diffusion through muscle cells and perhaps acting as an oxygen reservoir during periods of profound cellular hypoxia.[31]

Oxygen consumption and exercise

Maximal oxygen consumption (VO_2 max) decreases with increasing altitude. The determinants of VO_2 max at altitude have recently been reviewed.[32] Although it has been shown that at up to 6000 m a climber selects a level of activity at between 50 and 75% of their VO_2 max,[33] as altitude increases so the effort required for even simple physical tasks moves closer towards the maximal oxygen consumption, such that on the summit of Mount Everest the VO_2 max is around 1.2 L min^{-1}, a work rate equivalent to walking slowly on the flat.[34] The determinants of VO_2 max provide another useful method, like the oxygen cascade, of visualizing the limiting factors in the chain from ambient air to mitochondria. Figure 6 shows the calculated effect on the VO_2 max of a climber on the summit of Mount Everest of increasing certain determinants by only 5%. Conversely, decreasing barometric pressure by 5%, which would have the effect of raising the summit of Mount Everest by only 400 m, would reduce VO_2 max by around 25% to a value of less than 800 ml min^{-1}, rendering an ascent without supplementary oxygen almost certainly impossible.[35] It is a remarkable evolutionary coincidence that the summit of the world's highest mountain should lie just within the limits of man's physiological abilities to ascend it while still breathing its ambient atmosphere. The disease processes and hazards which may be encountered while at high altitude form the subject of the next article.

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