

# Respiratory Physiology at Altitude

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## Abstract

The changes in respiratory physiology that occur with increasing altitude are driven by the fall in the partial pressure of oxygen that occurs with decreasing barometric pressure. At altitude, respiratory system changes occur which impact on each step of the oxygen cascade that occurs within the body. These changes are pivotal to the process of acclimatisation to altitude. The study of human respiratory physiology at altitude has the potential to produce research that will be translational to disease states characterised by hypoxaemia.

## Introduction

The changes in respiratory physiology that occur with increasing altitude are driven by the fall in the partial pressure of oxygen that occurs with decreasing barometric pressure.

Dalton's Law states that the pressure exerted by a mixture of gases is equal to the sum of the pressures that each would exert if it alone occupied the space filled by the mixture (Box 1).

$$P_t = P_1 + P_2 + P_3 \dots P_n$$

Where  $P_t$  = total pressure

$P_1 + P_2 + P_3 \dots P_n$  = partial pressures of the constituent gases

### Box 1: Dalton's Law of partial pressures

Consequently it follows that the partial pressure of any gas in a mixture is derived by (Box 2):

$$P_x = F_x \times P_t$$

$P_x$  = partial pressure of any individual gas component of a mixture

$F_x$  = fractional concentration of gas x in the mixture

$P_t$  = total pressure of the gas mixture

### Box 2: Partial pressure of gases

Thus, although the percentage of oxygen in the atmosphere is constant (up to about 300 000 feet / 91440 metres), the partial pressure falls exponentially with increasing altitude and hence the molecular content of oxygen per unit volume of inspired gas falls similarly.

The effects of the consequent hypoxia on the human body are determined, in part, by the speed of onset of the hypoxia. A sudden exposure to the hypobaric hypoxia of high altitude, such as might occur with sudden decompression within an aircraft, would cause significant hypoxaemia resulting in neurological dysfunction and eventual loss of consciousness. The concept of 'time of useful consciousness' (Table 1) is familiar to aircrew and represents the time available to the operator to make reasoned decisions before they become debilitated.

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Altitude (ft/m)	Time of useful consciousness (seconds)
25,000 / 7620	270 (SD 96)
30,000 / 9100	145 (SD 45)
36,000 / 10,930	71 (SD 16)

Table 1: The time of useful consciousness up to 36,000ft (10,930m) [1]

By contrast, it is now more than 30 years since Peter Habeler and Reinholdt Messner became the first humans to reach the summit of Mt Everest (8848m) without supplementary oxygen. Every year thousands of tourists travel to mountainous areas for the challenge of climbing high. This provides a clear indication that where the human body is exposed to sustained hypoxia, physiological *acclimatization* can occur. High altitude regions of the world support millions of people living at altitudes above 3500m. The highest permanent human habitation is thought to be La Rinconada in southern Peru, at 5100m [2]. In these populations further physiological changes will have occurred. This is referred to as physiological *adaptation*.

At altitude, respiratory system changes occur which impact on each step of the oxygen cascade. A proportion of these changes are intended to maintain the oxygen flux to the mitochondria and thus contribute to acclimatization. The remaining changes constitute the pathological effects of high altitude on the respiratory system. It is useful to review oxygen transport under normal physiological conditions at sea level before considering the effect of increased altitude.

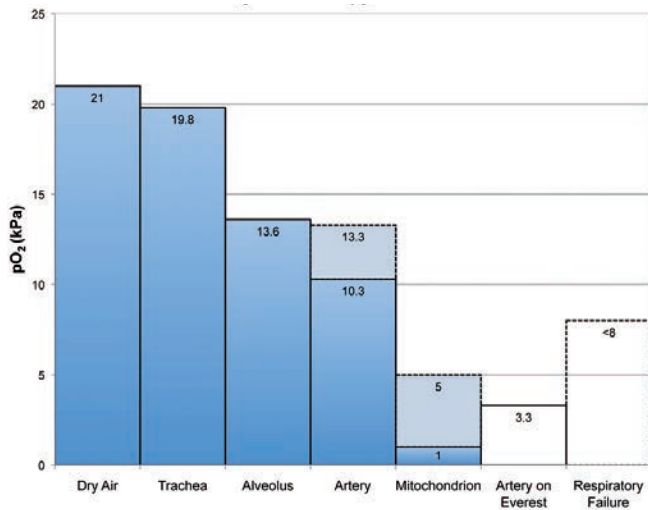
## Oxygen Transport

Oxygen is transported from the atmosphere to the tissues down its concentration gradient. This is known as the oxygen cascade (Figure 1). At each point the partial pressure of oxygen can be estimated [3].

Dry air at sea level where the barometric pressure is 1 atmosphere (101.325kPa) contains 20.95% oxygen. Thus the partial pressure of oxygen is an estimated  $(0.21 \times 100\text{kPa}) = 21\text{kPa}$ .

When air is inspired it is humidified and thus the partial pressure of oxygen is reduced by the water vapour content (6.3kPa). Thus the inspired partial pressure of oxygen is an estimated  $(0.21 \times (100\text{kPa} - 6.3\text{kPa})) = 19.8\text{kPa}$ .

At the alveolus, the oxygen is mixed with carbon dioxide. The ratio of the amount of carbon dioxide produced to oxygen consumed is determined by the respiratory quotient (RQ), which



**Figure 1:** The cascading partial pressure of oxygen through the respiratory system. The ranges for partial pressures are shown for arterial blood and the mitochondrion. ‘Artery on Everest’ shows the average value for the partial pressure of oxygen in the arterial blood of 4 climbers at 8,400m on their descent from the summit of Mt. Everest [12]. An oxygen partial pressure of < 8kPa is accepted as the threshold for respiratory failure.

for a person with a normal diet, at rest, is taken to be 0.8. Now the partial pressure of oxygen is determined by the alveolar gas equation (Box 3).

$$PAO_2 = PiO_2 - PACO_2 / RQ$$

PAO<sub>2</sub> = alveolar partial pressure of oxygen  
 PACO<sub>2</sub> = alveolar partial pressure of carbon dioxide (taken to be the same as arterial partial pressure)  
 PiO<sub>2</sub> = inspired partial pressure of oxygen

**Box 3: The alveolar gas equation**

Thus the alveolar partial pressure of oxygen is an estimated (19.8 – 5/0.8) = 13.6kPa.

Gas exchange occurs at the alveolar-capillary interface with oxygen (and carbon dioxide) moving across this very thin membrane (typically 0.5 micrometres thick) by diffusion down its partial pressure gradient. The total area available for gas exchange is a huge 50-100m<sup>2</sup> as a result of the vast number of alveoli in the normal lung (typically 300 million): the resistance to gas diffusion between the gas and blood phases is consequently very low. Oxygenated blood from the pulmonary circulation is mixed with a small amount of blood in the arterial system that will have bypassed oxygenated alveoli. This is known as venous admixture or physiological shunt and consists of blood from the bronchial circulation, Thebesian vessels (cardiac veins draining directly into the cardiac cavities) and blood that has passed areas of poor ventilation.

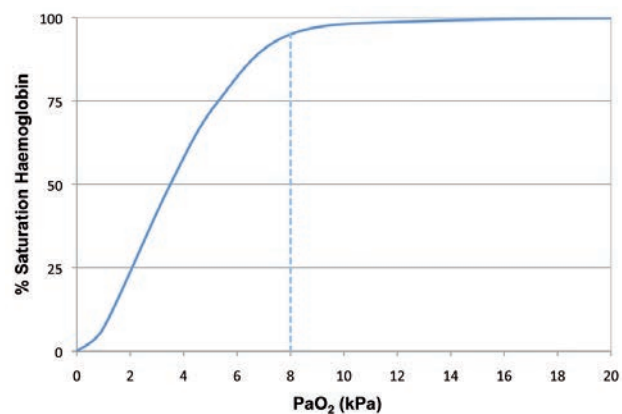
The reference value for the partial pressure of oxygen in arterial blood (PaO<sub>2</sub>) is 10.3kPa to 13.3kPa. Beyond childhood, there is a progressive reduction with increasing age [4]. At tissue level oxygen diffuses from capillary blood and ultimately reaches the mitochondria within the cells where cellular respiration occurs. At this point the partial pressure of oxygen is 1 – 5kPa. The mitochondrion will continue to respire aerobically until the partial pressure of oxygen falls below the Pasteur Point. This is thought to be 0.15-0.3kPa [5].

**Effects of altitude**

**Ventilation**

Ventilation is regulated by three stimuli; carbon dioxide (CO<sub>2</sub>), oxygen and pH. These stimuli are sensed and transduced by peripheral and central chemoreceptors. The efferent response is co-ordinated by the medullary respiratory centres [6]. Changes within this system must occur at altitude to facilitate survival in the hypobaric hypoxic environment.

The aortic and carotid bodies are the peripheral chemoreceptors. These clusters of chemoreceptor (glomus Type 1) and supporting cells are distributed in the aortic arch and just above the carotid bifurcation respectively. In humans, the carotid bodies are the dominant peripheral receptors. The carotid bodies are highly vascularised – receiving the highest blood flow per 100g tissue in the body [5]. Thus they are stimulated by the partial pressure of oxygen dissolved in the blood and increase ventilation only in hypoxic environments. They do not respond to low oxygen delivery states related to anaemia or poor cardiac output, where increased ventilation would not improve tissue hypoxia. At oxygen partial pressures above 13.3kPa the receptors produce very little output; however, as the partial pressure falls below 8kPa output increases rapidly. This makes good protective, physiological sense when one considers that the oxygen dissociation curve steepens acutely at an oxygen partial pressure below 8kPa (Figure 2).



**Figure 2:** The oxyhaemoglobin dissociation curve describes arterial blood at 100% haemoglobin saturation with a partial pressure of oxygen of 13.3kPa, venous blood with a haemoglobin saturation of 75% corresponding to a partial pressure of oxygen of 5.3kPa and the P<sub>50</sub> (50% haemoglobin saturation) at 3.5kPa. The curve is sigmoid because haemoglobin exhibits cooperative binding of oxygen. Below 8kPa the % saturation of haemoglobin falls sharply – this corresponds to an increased output by the chemoreceptors within the carotid body which effects an increase in ventilation.

The carotid bodies’ afferent nerve fibres travel in the carotid sinus nerve and those of the aortic bodies with the vagus nerve. Both relay information to the cardiorespiratory centre in the medulla. The effector response to the detected hypoxia is increased ventilation. The resulting increased minute volume serves to reduce alveolar partial pressure of carbon dioxide. By referring back to the alveolar gas equation, it can be seen that by reducing the partial pressure of carbon dioxide at the alveolus, the partial pressure of oxygen will be increased. This acute and reversible increase in ventilation induced by hypoxia is the key respiratory change associated with environmental hypoxia, and is termed the hypoxic ventilatory response (HVR).

The HVR is not maintained post hypoxic exposure. It is followed by the hypoxic ventilatory decline (HVD), whereby minute ventilation declines and the partial pressure of carbon dioxide is allowed to rise [7,8]. This occurs for a short period of less than one hour and then ventilation continues to increase again. At altitude this increased ventilation occurs for up to two weeks, and at a decreasing rate [9].

The peripheral chemoreceptors also respond to the partial pressure of carbon dioxide via its effect on the concentration of  $H^+$  ions, but less so than to oxygen partial pressure. The response to pH, and by extension carbon dioxide, is largely regulated by the central chemoreceptors. These chemoreceptors are on the ventrolateral surface of the medulla. They respond to pH changes in the cerebrospinal fluid (CSF).

As plasma carbon dioxide levels rise the gas diffuses freely into the CSF and increases the concentration of  $H^+$  ions. The blood brain barrier is much less permeable to  $H^+$  ions and bicarbonate than it is to carbon dioxide. Thus changes in the partial pressure of carbon dioxide in arterial blood are reflected quickly in the CSF. The effector response of the central chemoreceptors is to increase ventilation via stimulation of the medullary respiratory centre. This is the hypercapnic ventilatory response (HCVR).

Prolonged exposure to the hypoxia of altitude causes a respiratory alkalosis the result of this would ordinarily be to reduce respiratory drive via the peripheral chemoreceptors. Renal compensation occurs and  $HCO_3^-$  is excreted in the urine. Subsequent loss of  $HCO_3^-$  from the plasma creates a concentration gradient of  $HCO_3^-$  from CSF to plasma and  $HCO_3^-$  moves out of the CSF. This reduction in CSF  $HCO_3^-$  causes an increase in free  $H^+$  ions in the CSF – this stimulates the central chemoreceptors and effects an increase in ventilation to reduce  $CO_2$  levels and hence  $H^+$  levels within the CSF. Physiologically this occurs to ensure that CSF pH remains constant. For a given sensitivity of the central chemoreceptors to  $H^+$ , the level of  $CO_2$  at which increased ventilation will occur has now been reset, to a lower level. The HCVR response has been shifted to the left [10]. Hypotheses pertaining to the aetiology of the reduction in CSF  $HCO_3^-$  also include reference to hypoxia driven acidosis causing a reduction in CSF pH, which would reduce the available  $HCO_3^-$  as it was consumed for buffering purposes. Current consensus of opinion considers the HVR to be of more importance than HCVR in the hyperventilation of altitude acclimatization [11].

### Summary of Ventilation Effects

HVR stimulates an increase in ventilation on acute exposure to a hypoxic environment. This is necessary for survival and is mediated in the most part by the response of the carotid body. The resultant hypocapnia blunts the ventilatory response as dictated by the HCVR. HVD occurs, its aetiology is unclear. With ongoing exposure to hypoxia, ventilation remains augmented and the HVR is sensitized. Individuals who are acclimatized in this way will increase ventilation even with a modest increase in altitude. The mechanism for this is likely to be multifactorial. In contrast, those who are not acclimatized may have no increase in ventilation up to altitudes of 3500m.

### Diffusion

Diffusion of oxygen (and  $CO_2$ ) across the alveolar and capillary membranes is governed by Fick's Law of diffusion and each gas moves down its concentration gradient. Under normal environmental conditions the oxygen content of pulmonary

capillary blood increases rapidly such that there is near equalisation of alveolar and capillary  $PO_2$  by the time the blood has transited one third of the total distance it will travel through the alveolar bed [3]. The characteristics of the blood-gas barrier are optimal for diffusion and there is no diffusion limitation to gas transfer. Equilibrium will be reached between the partial pressures of gases in the alveolus and pulmonary capillary. The rate of gas exchange can only be increased by increasing pulmonary blood flow – there is *perfusion* limitation.

At altitude there is *diffusion* limitation. Diffusion of oxygen into the capillary occurs along the entire length of its communication with the alveoli. Despite this, there is a failure to reach equilibrium between alveolar and capillary  $PO_2$  at the end pulmonary capillary. This is exacerbated by exercise at altitude as cardiac output increases and the time that the red blood cell spends adjacent to the alveoli in the pulmonary circulation is shortened. In the case of diffusion limitation, increasing the partial pressure of oxygen within the alveolus will increase gas exchange.

### Life at the limit

Recent research has produced analysis of the arterial blood of four climbers at 8,400m on their descent from the summit of Mt Everest. Weather conditions prevented the climbers from taking samples on the summit. The blood was taken from the femoral artery, protected and immediately transported by a Sherpa to 6,400m where it was analysed. The average  $PaO_2$  was 3.3kPa and  $PaCO_2$  1.8kPa [12]: a stark demonstration of the human body functioning at its limit. The samples also revealed alveolar-arterial oxygen differences much higher than would be predicted by theoretical calculations. The investigators suggest that this increased difference could be due to shunting, ventilation-perfusion mismatch or pulmonary diffusion limitation. It is speculated that the results could be related to sub-clinical high altitude pulmonary oedema. Figure 1 shows the  $PaO_2$  values in the context of the oxygen cascade and clinically recognised values for respiratory failure. Previous attempts to quantify oxygen partial pressures at the limit of survival include the analysis of end expiratory gases on the summit of Everest in 1981 – the estimated  $PaO_2$  using Bohr integration was 3.73kPa [13].

### Pulmonary Circulation

Pulmonary vascular resistance (PVR) increases in response to low alveolar partial pressures of oxygen. This occurs on acute exposure to hypoxia, in the acclimatized and in those living at altitude [14]. This is hypoxic pulmonary vasoconstriction.

The hypoxia of altitude causes a global pulmonary constriction. This is not known to contribute positively to the acclimatization process and is considered the core aetiological factor in high altitude pulmonary oedema [15].

### Ventilation and Perfusion Matching

The relationship between the ventilation of an alveolus and the blood flow through its adjacent capillaries determines the degree to which gas exchange can take place. It follows that matching of perfusion and ventilation throughout the lung is necessary for efficient gas exchange. The upper part of the lung is the least well perfused due to the effect of gravity. This area of the lung, West zone 1, has a high ventilation to perfusion (V/Q) ratio. The increase in flow of blood with distance from the apex produced by gravity is much greater than the corresponding increase in ventilation; therefore, the ventilation to perfusion ratio decreases

with distance from the apex and is lowest at the base. Here, in West zone 3, the V/Q ratio is 0.6. As a whole, the lung has an overall V/Q ratio of 0.8 [3]. At sea level ventilation/perfusion mismatching plays a significant role in tissue hypoxia associated with lung pathology. With increasing altitude there is some evidence that the unequal distribution of blood flow related to gravity is improved. This is postulated to be an effect of the increased pulmonary blood flow occurring as a result of hypoxic pulmonary vasoconstriction. The overall effect that the improved uniformity of blood flow throughout the lung has on gas exchange is presumed to be minimal [16].

### Periodic Breathing

Nocturnal periodic breathing is very common at high altitude and occurs more frequently with increasing altitude. Chemoreceptor responses are altered during sleep. The hypoxic subject hyperventilates until an apnoeic CO<sub>2</sub> threshold is reached at which point ventilation ceases until oxygen levels fall sufficiently low to stimulate breathing. Thus the oxygen saturations and heart rate oscillate with ventilation. The breathing pattern is characterised by repeated episodes of hyperpnoea alternating with apnoea [15]. The clinical picture is identical to Cheyne-Stokes breathing seen in cardiac failure patients. At altitude the cycle time is shorter than that seen in cardiac failure, due to the increased circulation time. Recent research investigating periodic breathing in children showed that they had shorter cycles of periodic breathing than adults. This reflects the child's shorter circulation time [17]. The attendant cycles of apnoea, air hunger and deep breathing occurring with periodic breathing are disruptive to sleep and contribute to the poor quality of sleep experienced at altitude [18].

### Mountain-side to bed-side – applications for respiratory disease?

Altitude based research may reveal novel insights into mechanisms of respiratory disease. By studying otherwise healthy populations at altitude the physiological and genetic differences between those who adapt well to altitude and those who do not, can be used to guide research [19]. For example, the hypoxia associated with both hypobaric exposure and respiratory disease stimulates altered gene expression via hypoxia-inducible factor (HIF)-1 [20]. Numerous cellular processes are regulated by HIF-1, including glycolytic enzymes and the leptin gene. COPD patients are known to have raised leptin levels, which increase at times of disease exacerbation [21]. The study of altitude related weight loss in healthy subjects may elucidate the intervening mediators between HIF-1 and leptin and further characterise the COPD process. Another interesting observation is the improvement in exercise capacity in patients with right heart failure and those at altitude when administered sildenafil [22,23]. The pulmonary dilator effects of sildenafil alone do not provide an adequate explanation for this observation since the altitude group showed no change in pulmonary haemodynamics. It is postulated that altered reactive oxygen species (ROS) metabolism and nitric oxide synthase production may be responsible for the effect, which provides further insight into the effect of sildenafil on patients with disease states [19].

### Summary

Survival at high altitude demonstrates the ability of the human body to acclimatise to an hypoxic environment. The changes within the respiratory system are pivotal to the overall acclimatisation process. The study of human physiology at high

altitude provides a unique opportunity to investigate the effects of hypoxia in otherwise healthy subjects and represents great potential for application to clinical practice.

### References

1. Gradwell DP. Hypoxia and hyperventilation. In: Rainford DJ, Gradwell DP (eds) *Ernsting's Aviation Medicine* 4<sup>th</sup> Edn. London: Hodder Arnold, 2006; Ch 3
2. West JB. Highest permanent human habitation. *High Alt Med Biol* 2002; **3**: 401-7
3. West JB. *Respiratory Physiology. The Essentials* 7<sup>th</sup> Edn. Baltimore, USA: Lippincott, Williams & Wilkins, 2005
4. Dodds C, Kumar C, Servin F. *Anaesthesia for the Elderly Patient (Oxford Anaesthesia Library)*. Oxford: Oxford University Press, 2007
5. Yentis S, Hirsch N, Smith G. *Anaesthesia and Intensive Care A-Z* 4<sup>th</sup> Edn. London: Churchill Livingstone, 2009
6. Pocock G, Richards C. *Human Physiology. The Basis of Medicine* 3<sup>rd</sup> Edn. Oxford: Oxford University Press, 2006
7. Vovk A, Smith WDF, Paterson ND, Cunningham DA, Patterson DH. Peripheral chemoreceptor control of ventilation following sustained hypoxia in young and older adult humans. *Exp Physiol* 2004; **86**: 647-56
8. Garcia N, Hopkins SR, Elliott AR et al. Ventilatory response to 2 hour sustained hypoxia in humans. *Respir Physiol* 2001; **124**: 11-22
9. Smith CA, Bisgard GE, Nielsen AM et al. Control of breathing at high altitude. In: Hornbein TF, Schoene RB (eds) *Lung Biology in Health and Disease, Vol 161*. New York: Marcel Dekker, 2001; pp.140-8
10. Kellogg RH. The Role of CO<sub>2</sub> in altitude acclimatization. In: Cunningham DJC, Lloyd BB (eds) *The Regulation of Human Respiration*. Oxford: Blackwell Scientific Publications; pp.379-94
11. West B, Schoene R, Milledge J. *High Altitude Medicine and Physiology* 4<sup>th</sup> Edn. London: Hodder Arnold, 2007; Ch 5
12. Grocott M, Martin D, Levett D, McMorrow R, Windsor J, Montgomery H. Arterial Blood Gases and Oxygen Content in Climbers on Mount Everest. *N Engl J Med* 2009; **360**: 140-9
13. West JB, Hackett PH, Maret KH et al. Pulmonary gas exchange on the summit of Mt. Everest. *J Appl Physiol* 1983; **55**: 678-87
14. West B, Schoene R, Milledge J. *High Altitude Medicine and Physiology* 4<sup>th</sup> Edn. London: Hodder Arnold, 2007; Ch 7
15. Pollard A, Murdoch D. *The High Altitude Medicine Handbook* 3<sup>rd</sup> Edn. Abingdon, UK: Radcliffe Publishing Ltd, 2003
16. West B, Schoene R, Milledge J. *High Altitude Medicine and Physiology* 4<sup>th</sup> Edn. London: Hodder Arnold, 2007; Ch 6
17. Kohler M, Kremler S, Wilhelm EM, Brunner-LaRocca H, Zehnder M and Bloch KE. Children at high altitude have less nocturnal breathing than adults. *Eur Respir J* 2008; **32**: 189-197
18. Weil JV. Sleep at high altitude. *High Alt Med Biol* 2004; **5**(2): 180-9
19. Khosravi M, Grocott M. Mountainside to bedside: reality or fiction? *Expert Rev Resp Med* 2009; **3**(6): 561-565
20. Semenza GL, Agani F, Iyer N et al. Hypoxia inducible factor – 1: from molecular biology to cardiopulmonary physiology. *Chest* 1998; **114**: 40s-45s
21. Takabatake N, Nakamura H, Abe S et al. Circulating leptin in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; **159**(4): 1215-1219
22. Blum A. Treating heart failure with sildenafil. *Congest Heart Fail* 2009; **15**(4): 181-185
23. Faoro V, Lamotte M, Deboeck G et al. Effects of sildenafil on exercise capacity in hypoxic normal subjects. *High Alt Med Biol* 2007; **8**(2):155-163