

The mechanics and control of ventilation

Nick P Talbot

Thomas G Smith

Keith L Dorrington

Abstract

The lungs are responsible for oxygenating the blood and removing carbon dioxide from the body. They are also responsible for a very substantial burden of disease in the UK and worldwide population, and for the cancellation or complication of many surgical procedures. This brief article reviews the basic mechanics of the respiratory system, and highlights some of the important and interesting aspects of the regulation of ventilation, focussing on the role of the peripheral and central chemoreceptors. A sound knowledge of this basic respiratory physiology and pathophysiology is a prerequisite for effective preoperative assessment and good perioperative care.

Keywords carbon dioxide; carotid body; chemoreceptors; hypoxia; oxygen; ventilation

Ventilation

Ventilation (\dot{V}_E) is the volume of gas expired from the lungs in 1 minute. Of this volume, usually about 6 litres/minute, some is simply damp air leaving the upper 'dead space' of our airway and plays no role in gas exchange. Most of the gas breathed out, the 'alveolar ventilation' (\dot{V}_A , ~ 4 litres/minute), carries carbon dioxide at a concentration (strictly a fraction, equal to ~ 0.05) that equals $P_{A_{CO_2}}/P_{atm}$, where $P_{A_{CO_2}}$ is the partial pressure of carbon dioxide in the alveoli and P_{atm} is the total pressure of gas in the alveoli, which can be taken to be the same as atmospheric pressure (~ 101 kPa). The central relationship of ventilatory control is the following: in the steady state the volume of carbon dioxide generated by the body's metabolism in 1 minute (\dot{V}_{CO_2}) has to equal the volume of carbon dioxide breathed out of the

alveoli in that time, which in turn must equal the volume of gas leaving the alveoli times the fraction of that gas that is carbon dioxide. In short:

$$\dot{V}_{CO_2} = \dot{V}_A \times (P_{A_{CO_2}}/P_{atm}) \quad (1)$$

Or, rearranging the equation:

$$P_{A_{CO_2}} = (\dot{V}_{CO_2} \times P_{atm}) / \dot{V}_A \quad (2)$$

Typical numbers in equation 2 for an adult at rest would be

$$5 \text{ kPa} = (0.2 \text{ litres/minute} \times 100 \text{ kPa}) / (4 \text{ litres/minute})$$

with the volumes of gases measured at body temperature and ambient atmospheric pressure, though one should note that other reference temperatures and pressures are sometimes used.

In healthy lungs, and in many disease states, the level of carbon dioxide in arterial blood ($P_{a_{CO_2}}$) is very close to $P_{A_{CO_2}}$, because the lungs are extremely efficient at bringing pulmonary blood into equilibrium with alveolar gas. In most circumstances $P_{a_{CO_2}}$ appears to be the primary controlled variable and equation (2) describes the feedback system by which the blood level of carbon dioxide can be altered by changing ventilation. The question of why $P_{a_{CO_2}}$ is maintained very close to 5.3 kPa in most healthy volunteers remains a mystery, but it is interesting to note that this 'set-point' of ventilatory control can be altered by respiratory disease, or by physiological challenges such as ascent to high altitude (see 'Adaptation in the chemical control of ventilation' below).

Mechanics of ventilation

The minimum requirement for effective ventilation is an intact neurological drive to competent respiratory skeletal muscle working via a structurally sound thoracic cage combined with patent upper and lower airways. The normal intrapleural pressure is approximately 0.5 kPa below atmospheric pressure, reflecting the balance between the inward tug of the elastic tissue of the lung and the outward retraction of the structures of the chest wall. Historically, it was the disruption of this balance by surgical thoracotomy that led in 1896 to the introduction by the French surgeons Tuffier and Hallion of endotracheal insufflation of gas to prevent lung collapse. The Germans had a different approach. In 1904 Sauerbruch conceived a whole operating room that was held at a subatmospheric pressure, with only the patient's head held outside the room at normal atmospheric pressure, whilst Brauer in 1905 preferred to contain only the patient's head in a box at a pressure higher than atmospheric; in both cases, an airtight seal around the neck provided a tricky challenge. None of these approaches permitted proper cyclical ventilation of the lungs with gas. In modern surgical practice, neuromuscular blockade is used to produce muscle paralysis (including the respiratory muscles) in perhaps 50% of patients undergoing surgery. This iatrogenic form of complete ventilatory failure is managed with cyclical positive pressure ventilation of the lungs via some kind of airway device, commonly an endotracheal tube.

In a healthy individual breathing spontaneously, the tidal volume of each breath at rest is about 0.5 litres, with the first third of that expired volume coming from the airway dead space

Nick P Talbot *BM BCH DPhil MRCP* is an Academic Clinical Fellow in Respiratory Medicine at the Churchill Hospital, Oxford, and a Junior Research Fellow at St Peter's College, Oxford, UK. Conflicts of interest: none declared.

Thomas G Smith *MBBS DPhil FRCA* is an Academic Clinical Fellow in Anaesthetics in the Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford, and a Junior Research Fellow at University College, Oxford, UK. Conflicts of interest: none declared.

Keith L Dorrington *DM BCH DPhil FRCA* is a Lecturer in Physiology at the University of Oxford, an Honorary Consultant in the Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford, and a Fellow of University College, Oxford, UK. Conflicts of interest: none declared.

and two-thirds coming from the alveoli. Healthy adults have an excursion (vital capacity) from full inspiration to maximal expiration of 4–5 litres, after which a residual volume of about 1.5 litres remains in the lungs. A reduction in vital capacity to below 1 litre represents a severe restrictive impairment to ventilation. A reduction in the ability to breathe out over 85% of the vital capacity in 1 second is a measure of airway obstruction. This is also commonly quantified by measuring the peak expiratory flow that can be achieved after taking a deep breath in. It is normally 400–500 litres/minute, but can be much lower in patients with asthma or other forms of obstructive lung disease.

A large variety of conditions are associated with failure of ventilation (Box 1), many of which are commonly encountered in surgical practice. Trauma and poisoning are notable for targeting the ventilatory apparatus at all levels. Examples include: head injury, phrenic nerve (C3, 4, 5) transection from a stab wound to the neck, nerve gas compounds, pneumothorax, flail segment, burn contractures.

It was the poliomyelitis epidemics in Europe in the early 1950s that stimulated the setting up of intensive care wards for artificial ventilation of patients in the acute phase of ventilatory failure; an astounding reduction in mortality was associated with either negative pressure ventilation (the so-called ‘iron lung’ used widely in British hospitals) or with positive pressure ventilation (favoured by Scandinavians). Both medical and surgical intensive care remain heavily dependent on therapeutic controlled ventilation.

Alveolar mechanics and active epithelial transport

In 1987 animal experiments by Basset and colleagues first clearly showed that the epithelial cells lining the alveoli of the adult lung

pump sodium and glucose, followed by water, out of the alveoli into the interstitium of the lung. The equivalent flow of liquid from adult human lungs is probably up to 2 litres/day. The lung therefore absorbs actively, somewhat like the gut, from which it is derived embryologically. This discovery has reignited a debate relating to the longstanding notion that the lungs are lined with liquid, and that the largely phospholipid nature of surfactant reduces the surface tension of this huge water-air interface, thereby making the lungs compliant enough for normal breathing to occur. This view now seems overly simplistic. Surfactant is certainly essential to prevent the lungs becoming stiff, oedematous, and collapsed, or atelectatic. The question that is taxing us at present is whether the active epithelial absorption of sodium is also an essential component of healthy alveolar mechanics. There is some evidence to suggest that patients in intensive care clear pulmonary oedema faster if the sodium absorption mechanism is lively. In addition, an important trial from Switzerland in 2002 showed that, in 33 climbers known to be susceptible to high-altitude pulmonary oedema, prophylactic treatment with the inhaled β_2 -adrenoceptor agonist salmeterol reduced the incidence of oedema at 4,559 m by more than 50%.¹ Salmeterol and other β_2 agonists stimulate the alveolar absorption mechanism, and this trial was the first clear case of active alveolar liquid absorption being able to tip the balance between health and disease.

Lung mechanics during surgery and anaesthesia

Atelectasis, with reduced lung compliance, was shown in 1986 by Swedish researchers to be a common cause of impaired gas exchange in anaesthetized patients.² Computed tomography scans during anaesthesia showed large collapsed areas in the lowermost parts of the lungs. It appears that loss of respiratory muscle tone during anaesthesia leads to a substantial reduction in thoracic volume of around 0.5 litres; the lungs therefore shrink a bit, and the effect of gravity is to compress the dependent lung tissue. The effect can persist into the postoperative period, lead to hypoxaemia and predispose to respiratory infection. An intriguing question remains whether such collapse occurs during normal sleep.

Respiratory rhythm generation in the brainstem

The medulla oblongata contains numerous small nuclei of respiratory neurons that are broadly organized into dorsal and ventral respiratory groups. Each group contains neurons that oscillate their discharge rate according not only to integral ionic ‘pacemaker’ currents analogous to those of cardiac cells, but also in response to both excitatory (e.g. glutamate) and inhibitory (e.g. γ -aminobutyric acid (GABA), glycine) neurotransmitters released from nearby neurons. Current opinion suggests that at least six types of neurons, each with characteristic firing patterns, form a complex network within the brainstem to produce a cycle of breathing. However, this medullary pattern generator is subject to (and dependent upon) influences from other areas of the central nervous system, and via feedback from chemoreceptors.

Chemical control of ventilation

In 1885 Miescher-Rusch observed the exquisite sensitivity of ventilation to changes in levels of inspired CO_2 , and its relative insensitivity to moderate reductions in levels of inspired O_2 . He asserted that carbon dioxide ‘spreads its protective wings over the

Examples of conditions associated with ventilatory failure

Pharmacological

- General anaesthesia
- Opiate analgesia
- Neuromuscular blockade

Neurological

- Poliomyelitis

Neuromuscular

- Myasthenia gravis

Thoracic impairment

- Kyphoscoliosis

Diaphragm splinting

- Abdominal distention associated with ileus

Upper airway obstruction

- Laryngeal carcinoma

Lower airway obstruction

- Chronic obstructive pulmonary disease

Box 1

oxygen needs of the body'. This view has stood the test of time. We still believe that the P_{aCO_2} , detected at both central and peripheral chemoreceptors, is the primary controlled variable in the regulation of ventilation. In healthy individuals, hypoxia produces a significant increase in ventilation only when the arterial partial pressure of oxygen (P_{aO_2}) has fallen from a normal value of around 14 kPa to around 8 kPa. In contrast, a noticeable rise in ventilation is likely to occur if the P_{aCO_2} rises by only around 0.5 kPa.

The curse of Ondine

In German mythology the beautiful water-nymph Ondine, having found her husband in the arms of another, cast upon him a curse that condemned him to stop breathing upon falling asleep. Ondine's curse is the name often given to the so-called congenital central hypoventilation syndrome (CCHS), in which patients breathe relatively normally while awake, but hypoventilate during sleep, usually requiring overnight mechanical ventilation. They also lack ventilatory sensitivity to hypoxia or raised P_{aCO_2} (hypercapnia), even when awake, and seem not to experience the sensations of breathlessness normally associated with these stimuli. This failure of automatic respiratory control appears to be due to a lack of functional chemoreceptive feedback to the brainstem, and illustrates the absolute requirement of normal breathing for such feedback during sleep, but not during wakefulness. The aetiology of CCHS has recently been linked to expansion repeats in the *PHOX2B* gene, which is known to play an important role in autonomic neurogenesis within the brainstem and elsewhere.³

Central chemoreceptors

Around 85% of the ventilatory sensitivity to changes in P_{aCO_2} is mediated by central chemoreceptors. For many years researchers have searched in vain for the precise nature and location of these receptors. Recently, however, significant progress has been made. New techniques of immunohistochemistry, magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning have revealed that sensitivity to changes in CO_2 is not confined to a single discrete structure analogous to the peripheral chemoreceptor but is instead a more widespread phenomenon within the brainstem. The retrotrapezoid nucleus, medullary raphé, nucleus tractus solitarius and locus coeruleus are all sites at which experimental local acidosis (physiological changes in P_{CO_2} are very likely sensed in these areas as a change in pH) has been shown to produce appropriate changes in phrenic nerve discharge. A picture has emerged of an interconnected network of chemosensitive areas, analogous to (but probably separate from), the central respiratory rhythm generator itself. A considerable time-lag (~60 seconds) exists between a change of P_{aCO_2} and the stimulation of breathing by central chemoreceptors. This is likely to represent the time required for the change in P_{aCO_2} to produce a change in cerebrospinal fluid pH, to which the central chemoreceptors are thought to be most sensitive.

Peripheral chemoreceptors

In contrast to the central chemoreceptors, the location and anatomy of the major peripheral chemoreceptors are well known. The carotid bodies, located bilaterally close to the bifurcation of the carotid artery, were discovered by de Castro in 1926 and, largely on the basis of a disproportionately high blood flow relative to their own metabolic requirements, were immediately assigned a role in

'tasting' the arterial blood. It is now established that the carotid bodies mediate around 15% of the ventilatory response to increased P_{aCO_2} and almost all of the ventilatory sensitivity to hypoxia, responding very rapidly (within ~6 seconds) to changes in P_{aO_2} .

Each carotid body is composed of clusters of chemoreceptive glomus or type-1 cells, which are derived from the neural crest and form synaptic contacts with sensory fibres of the carotid sinus nerve. In response to an appropriate change in blood gas composition, the type-1 cell membrane is depolarized, probably via the inhibition of potassium channels. This depolarization leads to an increase in the calcium concentration within the type-1 cell, and the release of neurotransmitters (including acetylcholine, dopamine and adenosine triphosphate (ATP)) at the synapse.

The cellular mechanisms by which changes in P_{aO_2} and P_{aCO_2} are detected in the carotid bodies have been debated for many years. Historically, the type-1 cell mitochondrion was considered to be the primary site of cellular oxygen sensing. More recently, attention has been focused on a family of oxygen-sensitive potassium channels known as TASK channels. Membrane currents believed to be mediated by these channels have been identified in the membrane of type-1 cells isolated from rat carotid body, and are inhibited by both hypoxia and acidosis. TASK channels have also been implicated in the cellular mechanism of the central chemoreceptors.⁴ Given the profound inhibitory effect of anaesthesia on the ventilatory response to hypoxia and hypercapnia, it is of interest that these channels are also inhibited by inhalational anaesthetics.

Combined effects of CO_2 and O_2 on breathing

The quantitative relationship between ventilation and changes in P_{aCO_2} is shown in Figure 1. The steep linear relationship between P_{aCO_2} and ventilation reinforces once again the observation that very small changes of P_{aCO_2} have a large impact on breathing, while changes of P_{aO_2} within the 'physiological' range of 10–14 kPa appear to have little effect on ventilation. Lower levels of P_{aO_2} (<8 kPa), however, steepen the line considerably, indicating that the effects of hypercapnia and hypoxia on ventilation do not simply sum, but rather interact in a multiplicative manner. The site of this interaction is unclear. It could occur peripherally at the carotid body, or at the level of the brainstem, where afferent information from both central and peripheral chemoreceptors feeds back to the medullary respiratory centres.

Adaptation in the chemical control of ventilation

In healthy individuals, exposure to the hypoxia of high altitude produces a rapid increase in ventilation, due to stimulation of the carotid bodies. This so-called acute hypoxic ventilatory response (AHVR) initially minimizes the reduction in P_{aO_2} , helping to maintain arterial oxygen saturation, but produces a concomitant reduction in P_{aCO_2} (hypocapnia). According to the tight control of P_{aCO_2} described above, hypocapnia opposes the rise in ventilation, with the result that during the first few hours at altitude breathing is increased only moderately. Respiratory alkalosis is avoided, but at the expense of a large fall in arterial oxygen saturation, and therefore an increased risk of altitude-related illness such as acute mountain sickness (AMS) or high-altitude pulmonary oedema (HAPE).

Fortunately for mountaineers such as Reinhold Messner and Peter Habeler, who in 1978 became the first men to reach the

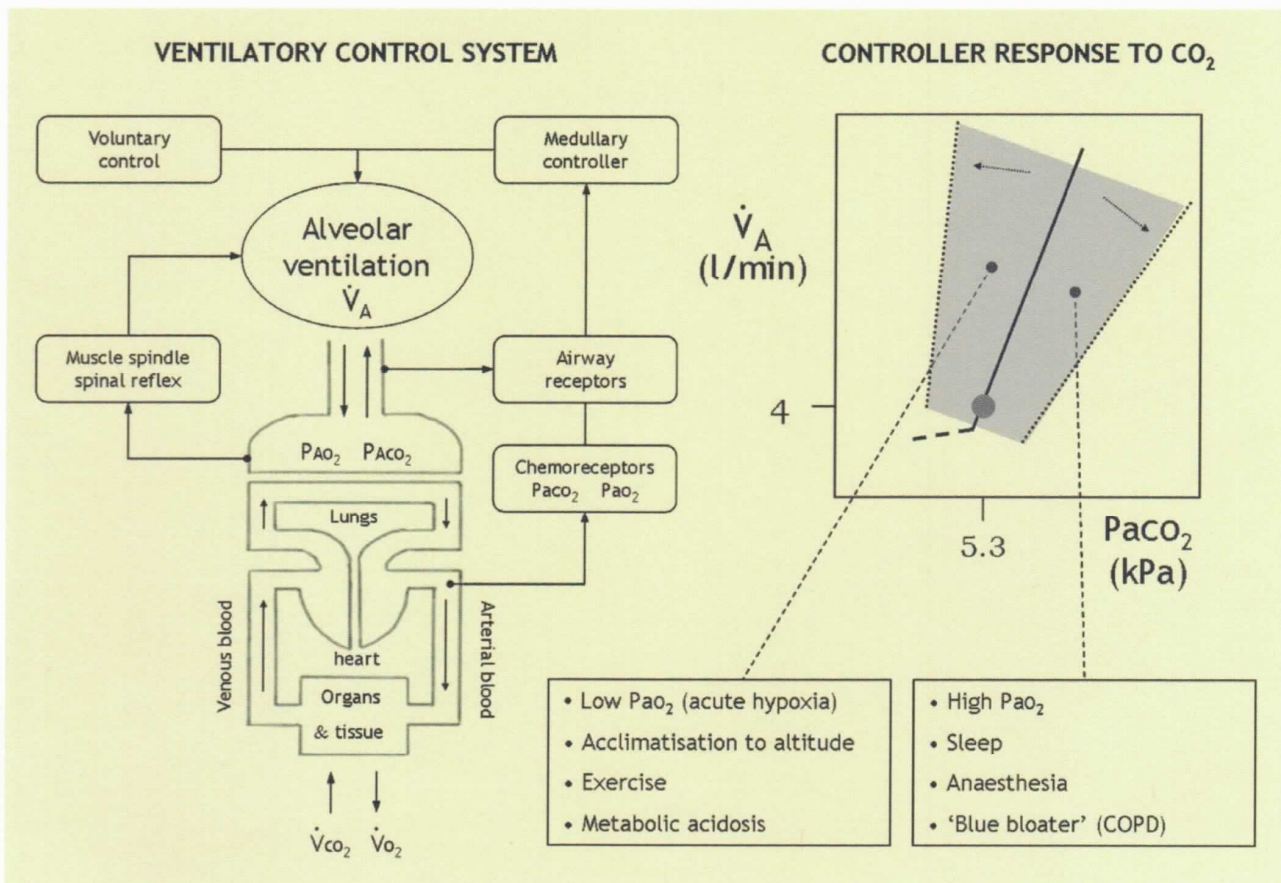


Figure 1 The left panel provides a schematic representation of the ventilatory control system, consisting of a respiratory output generated by a medullary controller and modulated by voluntary control mechanisms. The respiratory output determines alveolar ventilation, which sets the alveolar and arterial blood gas composition, and provides a feedback signal via the central and peripheral chemoreceptors. Ventilation can also be influenced by feedback from the muscle of the chest wall and receptors located within the airways. The right panel depicts the tight relationship between alveolar ventilation (\dot{V}_A) and the arterial partial pressure of carbon dioxide (Pa_{CO_2}). Boxes and arrows indicate factors that can alter the sensitivity of this relationship. The dotted 'dog-leg' at low values of ventilation (below around 4 litres/minute) represents the situation during wakefulness, when hypocapnia does not produce apnoea. During sleep or anaesthesia the linear relation between ventilation and Pa_{CO_2} is extended, and hypocapnia may cause breathing to stop entirely.

summit of Everest without using supplementary oxygen, the inhibitory effect of hypocapnia on ventilation at high altitude is not sustained. Instead, over a period of hours and days, ventilation (and therefore Pa_{O_2}) increases gradually. This process is possible because the respiratory system adapts, such that a progressively lower Pa_{CO_2} is tolerated by the ventilatory control system. In a recent study in which blood gas samples were taken from four climbers resting at an altitude of 8400 m on Everest, the mean Pa_{CO_2} was shown to be just 1.8 kPa.⁵ This value was associated with a mean Pa_{O_2} of 3.3 kPa, a value that would certainly have been even lower were it not for ventilatory acclimatization.

The mechanism of the apparent reduction in the 'set-point' of Pa_{CO_2} regulation in ventilatory acclimatization is likely to involve the gradual movement of bicarbonate out of the cerebrospinal fluid, returning the pH at the central chemoreceptors towards sea-level values. Over several days, an increase in bicarbonate excretion by the kidney also occurs, which might help to compensate for the respiratory alkalosis. In addition, the sensitivity of the carotid body to hypoxia gradually increases during sustained hypoxia, such that a given Pa_{O_2} will produce a greater hypoxic drive to breath in acclimatized individuals. The

mechanism of adaptation at the carotid body is not clear, but it seems likely to involve gene expression mediated by the hypoxia-inducible factor (HIF) family of transcription factors. This possibility is supported by observations in patients with rare diseases characterized by HIF dysregulation. Chuvash polycythaemia, for example, is an autosomal recessive condition caused by a specific mutation in the *VHL* gene, which leads to upregulation of HIF proteins and over-expression of hypoxia-regulated genes. Affected individuals not only develop excessive erythropoiesis and pulmonary hypertension, mimicking the effects of chronic hypoxia, but also display a reduction of Pa_{CO_2} and a marked increase in the respiratory sensitivity to hypoxia (AHVR), both cardinal features of ventilatory acclimatization to hypoxia.⁶

An example of less helpful adaptation within the chemical control of breathing is seen in some patients with longstanding CO_2 retention due to chronic obstructive pulmonary disease (COPD). In contrast to the effect of altitude, these patients display diminished respiratory sensitivity to hypercapnia, reduced renal bicarbonate excretion, and effectively an increased set-point of Pa_{CO_2} regulation. Such patients may be relying on concomitant hypoxia to produce a ventilatory drive, occasionally to such an extent that

administration of high flow oxygen, or the additional suppression of hypoxic drive seen during anaesthesia, can produce prolonged apnoea. The question of why some patients with COPD retain carbon dioxide in this way, while others maintain a vigorous effort to keep the P_{aCO_2} relatively normal, remains largely unanswered.

Control of ventilation by higher centres of the brain

The capacity for supra-brainstem regions of the brain to influence the control of ventilation is demonstrated by everyday activities such as eating and speaking. However, higher centres also appear to influence ventilation in more subtle ways.

'Wakefulness drive to breathe'

As mentioned above, patients lacking functional chemoreceptor feedback become apnoeic during sleep, but breathe fairly normally while awake. Similarly, if the P_{aCO_2} of healthy humans is reduced by mechanical ventilation during sleep or anaesthesia, apnoea will result, but a similar reduction of P_{aCO_2} during wakefulness leaves breathing relatively unaffected. In neither case is the subject required to 'remember' to breathe. Such findings have been interpreted as indicating that wakefulness *per se* may produce a stimulus to breathe. The precise neural substrate underlying this observation remains unclear, but the firing rate of some neurons in the medullary raphé has been shown to be dependent on both CO_2 levels and the state of arousal.

The locked-in syndrome

An indication that the 'wakefulness drive to breathe' is of cortical origin comes from patients with the locked-in syndrome, in whom the cortico-spinal or cortico-bulbar tracts are damaged (usually due to a stroke in the ventral pons), resulting in almost total loss of voluntary control of muscle movement. Such patients are completely conscious, and able to communicate by small movements of the eyes, but breathing is driven by the central rhythm generator with no component of voluntary control. In such patients, if P_{aCO_2} is reduced as described above, apnoea occurs even while awake, suggesting that the wakefulness drive is absent. Interestingly, however, emotions (such as laughter) can disturb the regular pattern of breathing, implicating sub-cortical regions of the brain in ventilatory control.

Mechanical feedback in the control of ventilation

The airways of the lung contain several types of receptor that are capable of influencing the respiratory rhythm. The main role of the pulmonary stretch receptors is the inhibition of inspiration in response to prolonged inflation of the lung, the so-called Hering-Breuer reflex. These receptors are important for control of ventilation in some animal species, but appear to play a limited role in humans. Irritant receptors, found on the epithelial surface

of the airways, are sensitive to both mechanical and chemical stimuli, and mediate bronchoconstriction in response to noxious stimuli. Fibres from these and other airway receptors return to the brainstem in the vagus nerve. In addition, the central nervous system receives mechanoreceptive feedback from muscle spindles within the ventilatory muscles.

Control of breathing during exercise

Despite detailed knowledge of many aspects of the ventilatory control system, we do not really understand how its various components interact. One of the longstanding unsolved mysteries of physiology is how the exercising body regulates ventilation so precisely in the presence of huge changes in \dot{V}_{CO_2} (up to ~ 12 times the value at rest) as to keep $P_{A_{CO_2}}$ and P_{aCO_2} close to 5 kPa. Figure 1 indicates the effect of exercise and some other factors on ventilatory control. ♦

REFERENCES

- 1 Sartori C, Allemann Y, Duplain H, et al. Salmeterol for the prevention of high-altitude pulmonary edema. *New Eng J Med* 2002; **346**: 1631–6.
- 2 Hedenstierna G, Tokics L, Strandberg A, Lundquist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. *Acta Anaesthesiol Scand* 1986; **30**: 183–91.
- 3 Amiel J, Laudier B, Attié-Bitach T, et al. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene *PHOX2B* in congenital central hypoventilation syndrome. *Nat Genet* 2003; **33**: 459–61.
- 4 Gestreau C, Heitzmann D, Thomas J, et al. Task2 potassium channels set central respiratory CO_2 and O_2 sensitivity. *PNAS* 2010; **107**: 2325–30.
- 5 Grocott MP, Martin DS, Levett DZ, et al. Arterial blood gases and oxygen content in climbers on Mount Everest. *New Eng J Med* 2009; **360**: 140–9.
- 6 Smith TG, Brooks JT, Balanos GM, et al. Mutation of von Hippel Lindau tumour suppressor and human cardiopulmonary physiology. *PLoS Med* 2006; **3**: e290.

FURTHER READING

- Crandall ED, Matthay MA. Alveolar epithelial transport: basic science to clinical medicine. *Am J Respir Crit Care Med* 2001; **163**: 1021–9.
- Guz A. Brain, breathing and breathlessness. *Respir Physiol* 1997; **109**: 197–204.
- Lumb AB. Nunn's applied respiratory physiology. 6th edn. Elsevier, 2005.
- Smith TG, Robbins PA, Ratcliffe PJ. The human side of hypoxia-inducible factor. *Br J Haematol* 2008; **141**: 325–34.
- Special issue. Central chemoreception. *Respir Physiol Neurobiol* 2010; **173**: 193–336.