# Respiration: control of ventilation

Emrys Kirkman


## Abstract

Rhythmic ventilation is an automatic process controlled by the central nervous system. Groups of cells in the brainstem, predominantly the ventral and dorsal respiratory groups, are responsible for generating basic respiratory rhythm. This basic rhythm is subject to modulation by both conscious and reflex actions. In normal individuals the respiratory minute volume is set to closely regulate arterial carbon dioxide tension ($PaCO_2$) at approximately 5.3 kPa, predominantly via a negative feedback reflex involving the central chemoreceptors. A separate group of chemoreceptors, the arterial chemoreceptors, are responsible for initiating the increased ventilatory response to counter arterial hypoxia, but a brisk response is not seen until $PaO_2$ levels fall to approximately 8.0 kPa from the normal 13.3 kPa. Combined hypercarbia and hypoxia (asphyxia) is a very powerful stimulus to breathe as the two inputs interact in a synergistic manner. The chemoreceptor reflexes can be modified when the need arises (e.g. blockade of the respiratory part of the arterial chemoreflex by the trigeminal reflex as part of the diving response). Other reflexes such as the Hering—Breuer reflex contribute to setting the balance between tidal volume and respiratory rate to attain a given minute volume, although this reflex does not appear to play a major role in humans at resting tidal volumes. Superimposed on this 'tonic' control, additional protective reflexes (e.g. from receptors in the upper airways) are recruited to protect the lungs and airways with responses such as coughs and sneezes when required.


**Keywords** Aortic bodies; arterial chemoreceptors; carotid bodies; central chemoreceptors; diving response; Hering—Breuer reflex; respiratory rhythm

## Learning objectives

After reading this article you should be able to describe the:

- neural arrangement that produces the basic respiratory rhythm
- short-term control of blood carbon dioxide, oxygen, pH and combined changes of these variables
- role of the peripheral chemoreceptors in controlling these variables, and of the central chemoreceptors when chronic hypoxia is present (at altitude)
- role of neural influences in regulating the chemoreceptor reflexes, as well as in regulating the rate and depth of ventilation

Ventilation is an automatic process that is controlled by the central nervous system. The brainstem is a key area responsible for the basic respiratory rhythm. This in turn is modulated by a number of influences ranging from conscious alterations (originating form 'higher centres'), tonic reflexes such as the chemoreceptor reflexes regulating carbon dioxide levels of the blood and preventing dangerous hypoxia to episodic reflexes such as coughing and sneezing.

## Origin of respiratory rhythm

The search for the area(s) of the brain and underlying mechanisms responsible for setting the basic respiratory rhythm has taken many years and is still continuing. Earlier ideas, based on experiments where gross changes in patterns of breathing were seen following transactions and focal lesions in the brainstem led to the concept of multiple respiratory 'centres' (e.g. apneustic and pneumotaxic centres), which interacted to provide respiratory rhythm. This type of concept is now outdated and the altered pattern of breathing seen in these experiments is now viewed as the result of general damage rather than disconnecting specific centres.

Control of ventilation is affected by clusters of neurones that are grouped in several distinct areas of the brainstem. Two such areas in the medulla are called the ventral respiratory group (VRG) and the dorsal respiratory group (DRG). Current thinking is that rhythm generation is the domain of a group of tightly clustered neurones in the VRG (specifically in the rostral ventrolateral medulla) called the pre Botzinger complex (PBC). Although the PBC is itself a complex area containing a heterogeneous population of neurones, the PBC neurones thought to be responsible for respiratory rhythmogenesis are all interneurones in the sense that they have no axons projecting out of the brainstem. PBC neurones then 'drive' groups of inspiratory neurones. A strong piece of evidence suggesting that the PBC neurones are indeed the respiratory rhythm generator is the finding that a small focal lesion in this area produces an immediate fatal apnoea. In addition, the VRG is viewed as being more important than the DRG in the generation of respiratory rhythm because the DRG has not been found in a number of species. The inspiratory neurones have a major output into the spinal cord and relevant cranial nuclei to influence the activity of relevant motorneurones. Other areas in the brain that influence the VRG (and DRG) are thought to modify the pattern of breathing, especially depth. One of these areas is the apneustic centre or Botzinger complex (Kolliker-fuse area) of the pons. Experimental evidence suggests that disruption of any of these areas (other than the PBC) will modify the depth or pattern of breathing, but will not abolish rhythmogenesis.

## Control of carbon dioxide tension in arterial blood

Carbon dioxide tension in arterial blood ($PaCO_2$) is very closely regulated around a set point (5.3 kPa or 40 mmHg in a healthy individual) by a negative feedback system. A rise in $PaCO_2$ stimulates a reflex increase in ventilation, excreting excess $CO_2$ and returning $PaCO_2$ to the set point. Conversely, a fall in $CO_2$ attenuates tonic respiratory drive, resulting in a fall in ventilation

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and accumulation of $CO_2$ until $PaCO_2$ has again reached normal levels (Figure 1). It is important to control $PaCO_2$ within such narrow limits because any alteration in $PaCO_2$ will in turn modify pH: hypercapnia causes a respiratory acidosis while hypocapnia causes a respiratory alkalosis. Significant changes in extracellular pH can lead to conformational changes in proteins such as enzymes and hence gross disturbances of body function.

The primary mechanism responsible for controlling $PaCO_2$ is a reflex originating from the central chemoreceptors. These chemoreceptors comprise a group of cells in the medulla of the brainstem, near the floor of the fourth cerebral ventricle (Figure 1b). The central chemoreceptors are separate and distinct from the cells generating respiratory rhythm, but the central chemoreceptors do normally provide a tonic respiratory 'drive'.

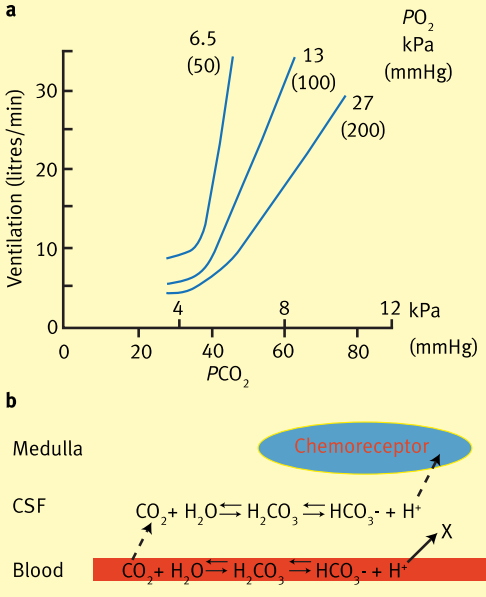
The predominant view is that the central chemoreceptors respond primarily to hydrogen ions ($H^+$) rather than directly to $CO_2$. In this scheme the $CO_2$ in the cerebrospinal fluid (CSF) leads to the generation of $H^+$ (Figure 1b) and stimulation of the chemoreceptors. Because the CSF contains few buffering proteins a change in $CO_2$ levels here causes greater alterations in $H^+$ levels than in the blood. Since $CO_2$ can cross the blood–brain barrier with ease, any change in blood $CO_2$ is fairly quickly reflected by an alteration in CSF $CO_2$, and ultimately a change in chemoreceptor activity. Although the same reaction (resulting in elevation of $H^+$ levels when $CO_2$ levels rise) takes place in the blood, the resulting $H^+$ in the blood is irrelevant for the central chemoreceptors because $H^+$ cannot diffuse across the blood–brain barrier in healthy individuals.

Having given the detailed description of the response of the central chemoreceptors to extracellular CSF $H^+$, it should be noted that some authors take a different view and argue that the central chemoreceptors respond to a change in intracellular $H^+$ levels resulting from an alteration in extracellular CSF $CO_2$ levels.

## Control of oxygen tension in arterial blood

Oxygen tension in arterial blood ($PaO_2$) is also controlled by a negative feedback reflex. However, $PaO_2$ is not regulated as sensitively as $PaCO_2$ until there has been a considerable fall in $PaO_2$ from the normal levels of approximately 13.3 kPa to about 8.0 kPa, beyond which there is a powerful increase in ventilation. Increases in $PaO_2$ above 13.3 kPa have little effect on ventilation (Figure 2), presumably because humans have not evolved with a threat of hyperbaric oxygen. One reason why this sort of control is appropriate for oxygen relates to the oxyhaemoglobin dissociation curve. Most of the oxygen in normal blood is bound

### The ventilatory response to hypercapnia at different values of $PO_2$

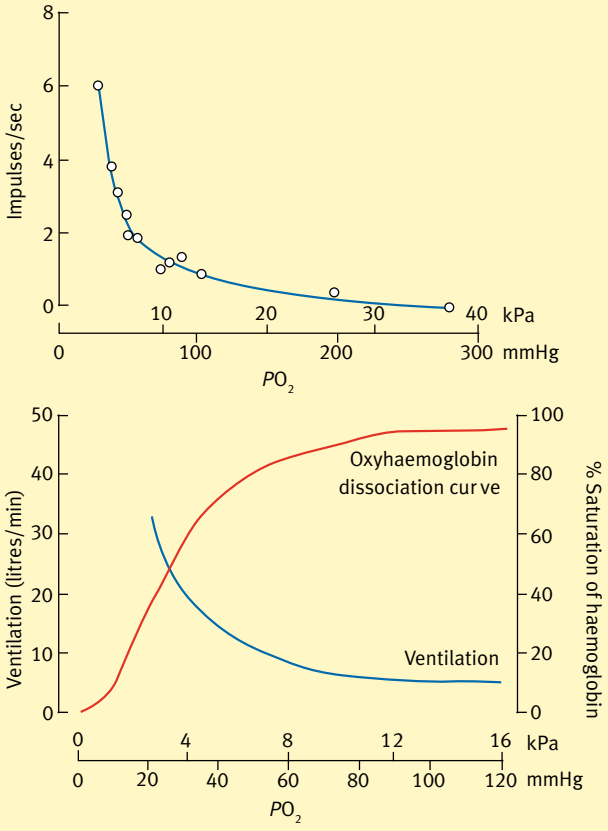



**a** Note that deviations of the partial pressure of carbon dioxide ($PCO_2$) from normal arterial levels elicit a brisk ventilatory response and that the sensitivity (slope) of the reflex increases when $PO_2$ is reduced, suggesting an interaction between the effects of hypoxia and hypercapnia.
**b** A schematic diagram indicating the mechanism whereby alterations in arterial carbon dioxide alters the stimulation to central chemoreceptors located near the floor of the fourth cerebral ventricle.

Figure 1a is reproduced from Pocock G, Richards CD. Human Physiology: the basis of medicine. Oxford: Oxford University Press, 2006.

**Figure 1**

### The effect of acute hypoxia




The effect of acute hypoxia on the discharge rate of arterial chemoreceptor afferent nerve fibres (upper graph) and pulmonary ventilation compared with the oxyhaemoglobin dissociation curve (lower graph).

Reproduced from Pocock G, Richards CD. Human Physiology: the basis of medicine. Oxford: Oxford University Press, 2006.

**Figure 2**