Update in
Anaesthesia

Originally published in Update in Anaesthesia, editions 2 (1992) and 12 (2000)

Respiratory Physiology

Fred Roberts*, Ian Kestin
*Correspondence Email: coolfred@btinternet.com

Summary

This article covers the main areas of respiratory physiology that are important to anaesthetists. Examples relevant to anaesthesia and pathological states of the respiratory system are used when possible. Further detail is included in the following articles on oxygen delivery and carbon dioxide transport. Some areas are covered in more than one article, but are included since alternative explanations from different authors may enhance understanding of more difficult aspects of this subject.

Fred Roberts
Consultant Anaesthetist
Royal Devon and Exeter
NHS Foundation Trust
Barrack Road
Exeter EX2 5DW
UK

Ian Kestin
Consultant Anaesthetist
Derriford Hospital
Derriford Road
Crownhill PL6 8DH
UK

INTRODUCTION

The main function of the lungs is to provide continuous gas exchange between inspired air and the blood in the pulmonary circulation, supplying oxygen and removing carbon dioxide, which is then cleared from the lungs by subsequent expiration. Survival is dependent upon this process being reliable, sustained and efficient, even when challenged by disease or an unfavourable environment. Evolutionary development has produced many complex mechanisms to achieve this, several of which are compromised by anaesthesia. A good understanding of respiratory physiology is essential to ensure patient safety during anaesthesia.

MECHANISM OF BREATHING

A pressure gradient is required to generate airflow. In spontaneous respiration, inspiratory flow is achieved by creating a sub-atmospheric pressure in the alveoli (of the order of –5cmH_2O during quiet breathing) by increasing the volume of the thoracic cavity under the action of the inspiratory muscles. During expiration the intra-alveolar pressure becomes slightly higher than atmospheric pressure and gas flow to the mouth results.

Motor pathways

The main muscle generating the negative intrathoracic pressure that produces inspiration is the diaphragm, a musculotendinous sheet separating the thorax from the abdomen. Its muscular part is peripheral, attached to the ribs and lumbar vertebrae, with a central tendon. Innervation is from the phrenic nerves (C3-5) with contraction moving the diaphragm downwards forcing the abdominal contents down and out. Additional inspiratory efforts are produced by the external intercostal muscles (innervated by their intercostal nerves T1-12) and the accessory muscles of respiration (sternomastoids and scalenes), although the latter only become important during exercise or respiratory distress.

During quiet breathing expiration is a passive process, relying on the elastic recoil of the lung and chest wall. When ventilation is increased (such as during exercise) expiration becomes active, with contraction of the muscles of the abdominal wall and the internal intercostals.

Central control

The mechanism by which respiration is controlled is complex. There is a group of respiratory centres located in the brainstem producing automatic breathing activity. This is then regulated mainly by input from chemoreceptors. This control can be overridden by voluntary control from the cortex. Breath-holding, panting or sighing at will are examples of this voluntary control.

The main respiratory centre is in the floor of the 4th ventricle, with inspiratory (dorsal) and expiratory (ventral) neurone groups. The inspiratory neurones fire automatically, but the expiratory ones are used only during forced expiration. The two other main centres are the apneustic centre, which enhances inspiration, and the pneumotaxic centre, which terminates inspiration by inhibition of the dorsal neurone group above.

The **chemoreceptors** that regulate respiration are located both centrally and peripherally. Normally, control is exercised by the central receptors located in the medulla, which respond to the CSF hydrogen ion concentration, in turn determined by CO_2, which diffuses freely across the blood-brain barrier from the arterial blood. The response is both quick and sensitive to small changes in arterial pCO_2 ($PaCO_2$). In addition, there are peripheral chemoreceptors located in the carotid and aortic bodies most of which respond to a fall in O_2, but some also to a rise in arterial CO_2. The degree of hypoxia required to produce significant activation of the O_2 receptors is such that they are not influential under normal circumstances, but will do so if profound hypoxia (PaO_2 < 8kPa) occurs, for example at high altitude when breathing air (see later in Special circumstances). It also happens when the response to CO_2 is impaired, which can occur if the $PaCO_2$ is chronically elevated, leading to a blunting of the central receptor sensitivity.

RESPIRATORY PROCESS

Respiratory values

The various terms used to describe lung excursion (movement) during quiet and maximal respiration are shown in Figure 1 below.

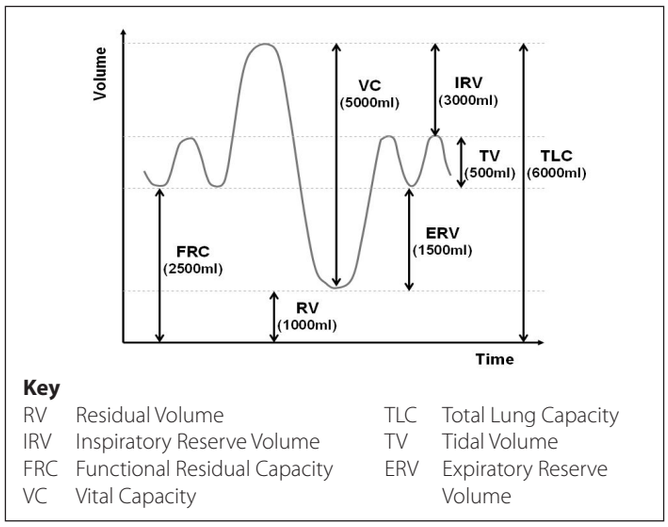

Figure 1. *Lung volumes in an adult male measured with a spirometer during quiet breathing with one maximum breath*

The tidal volume (500ml) multiplied by the respiratory rate (14breaths.min^{-1}) is the minute volume (7000ml.min^{-1}): TV x RR = MV. Not all of the tidal volume takes part in respiratory exchange, as this process does not start until the air or gas reaches the respiratory bronchioles (division 17 of the respiratory tree). Above this level the airways are solely for conducting, their volume being known as the anatomical deadspace. The volume of the anatomical deadspace is approximately 2ml.kg^{-1} or 150ml in an adult, roughly a third of the tidal volume. The part of the tidal volume which does take part in respiratory exchange multiplied by the respiratory rate is known as the alveolar ventilation (approximately 5000ml.min^{-1}).

Functional residual capacity (FRC) is the volume of air in the lungs at the end of a normal expiration. The point at which this occurs (and hence the FRC value) is determined by a balance between the inward elastic forces of the lung and the outward forces of the respiratory cage (mostly due to muscle tone). FRC falls with lying supine, obesity, pregnancy and anaesthesia, though not with age. The FRC is of particularly importance to anaesthetists because:

- During apnoea it is the reservoir to supply oxygen to the blood.
- As it falls the distribution of ventilation within the lungs changes leading to mismatching with pulmonary blood flow.
- If it falls below a certain volume (the closing capacity), airway closure occurs leading to shunt.

Resistance and compliance

In the absence of respiratory effort, the lung will come to lie at the point of the FRC. To move from this position and generate respiratory movement, two aspects need to be considered, which oppose lung expansion and airflow, and therefore need to be overcome by respiratory muscle activity. These are the airway resistance and the compliance of the lung and chest wall.

Resistance of the airways describes the obstruction to airflow provided by the conducting airways, resulting largely from the larger airways (down to division 6-7), plus a contribution from tissue resistance produced by friction as tissues of the lung slide over each other during respiration. An increase in resistance resulting from airway narrowing, such as bronchospasm, leads to obstructive airways disease. In obstructive airways disease, it might be expected that airflow could be improved by greater respiratory effort (increasing the pressure gradient) to overcome the increase in airways resistance. Whilst this is normally true for inspiration, it is not necessarily the case during expiration, as the increase in intrapleural pressure may act to compress airways proximal to the alveoli, leading to further obstruction with no increase in expiratory flow and air-trapping distally. This is shown in Figure 2 and demonstrates why expiration is usually the major problem during an asthmatic attack.

Compliance denotes distensibility (stretchiness) and in a clinical setting refers to the lung and chest wall combined, being defined as the volume change per unit pressure change (V/P). When compliance is low, the lungs are stiffer and more effort is required to inflate the alveoli. Conditions that worsen compliance, such as pulmonary fibrosis, produce restrictive lung disease. Compliance also varies within the lung according to the degree of inflation, as shown in Figure 2. Poor compliance is seen at low volumes (because of difficulty with initial lung inflation) and at high volumes (because of the limit of chest wall expansion), with best compliance in the mid-expansion range.

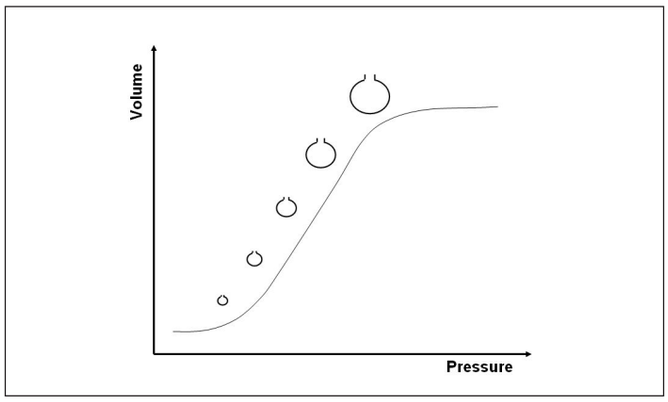

Figure 2. *Compliance curve showing compliance within the lung at different levels of inflation. At FRC in the young healthy individual the apices are well-inflated (towards the top of the curve) and therefore less ventilated than the midzones and bases, which are on the lower, steeper part of the compliance curve*

Work of breathing

Of the two barriers to respiration, airway resistance and lung compliance, it is only the first of these which requires actual work to be done to overcome it. Airway resistance to flow is present during both inspiration and expiration and the energy required to overcome it, which represents the work of breathing, is dissipated as heat.

Although energy is required to overcome compliance in expanding the lung, it does not contribute to the actual work of breathing as it is not dissipated, but converted to potential energy in the distended elastic tissues. Some of this stored energy is used to do the work of breathing produced by airways resistance during expiration. The work of breathing is best displayed on a pressure-volume curve of one respiratory cycle (Figure 3), which shows the different pathways

for inspiration and expiration, known as **hysteresis**. The total work of breathing of the cycle is the area contained in the loop.

With high respiratory rates, faster airflow rates are required, increasing the frictional forces. This is more marked in obstructive airways disease and such patients therefore generally minimise the work of breathing by using a slow respiratory rate and large tidal volumes. In contrast, patients with restrictive lung disease (poor compliance) reach the unfavourable upper part of the compliance curve soon, as the tidal volume increases. The pattern of breathing seen in such patients usually involves small tidal volumes and a fast respiratory rate.

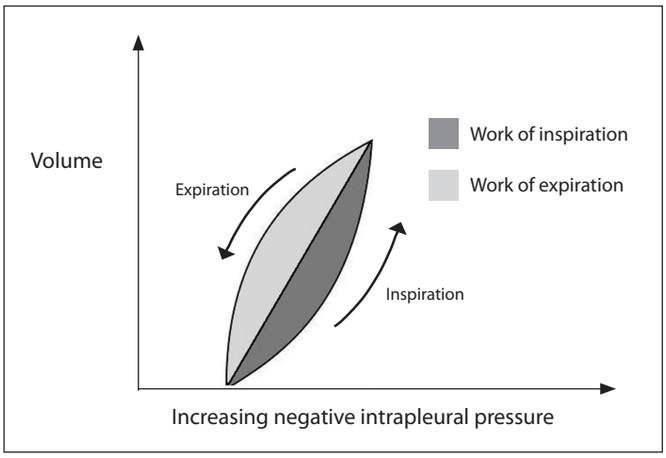

Figure 3. *Work of breathing shown on a lung pressure-volume (compliance) curve*

Surfactant

Any liquid surface exhibits surface tension, a tendency for the molecules on the surface to pull together. This is why, when water lies on a surface, it forms rounded droplets. If the surface tension is reduced, for example by adding a small amount of soap, the droplets collapse and the water becomes a thin film.

When a liquid surface is spherical, it acts to generate a pressure within the sphere according to Laplace's law:

$$\text{Pressure} = \frac{\text{2 x surface tension}}{\text{radius of sphere}}$$

The film of liquid lining the alveoli exhibits surface tension in such a manner to increase the pressure in the alveoli, with a greater rise in small alveoli than in large ones. Surfactant is a substance secreted by type II alveolar epithelial cells, which lowers the surface tension of this respiratory surface liquid markedly. Mainly consisting of a phospholipid (dipalmitoyl lecithin), its physiological benefits are:

- A reduction in the fluid leak from pulmonary capillaries into the alveoli, as the surface tension forces act to increase the hydrostatic pressure gradient from capillary to alveolus.
- An increase (improvement) in overall lung compliance.
- A reduction in the tendency for small alveoli to empty into large ones, reducing the tendency for the lung to collapse.

Diffusion of oxygen

The alveoli provide an enormous surface area for gas exchange with pulmonary blood (between 50-100m^2), with a thin membrane across which gases must diffuse. The solubility of oxygen is such that its diffusion across the normal alveolar-capillary membrane is an efficient and rapid process. Under resting conditions pulmonary capillary blood is in contact with the alveolus for about 0.75 seconds in total and is fully equilibrated with alveolar oxygen after only about a third of the way along this course. If lung disease is present which impairs diffusion, there is therefore still usually sufficient time for full equilibration of oxygen when at rest. During exercise, however, the pulmonary blood flow is quicker, shortening the time available for gas exchange, and so those with lung disease are unable to oxygenate the pulmonary blood fully and thus have a limited ability to exercise.

For carbon dioxide, which diffuses across the alveolar-capillary membrane 20 times faster than oxygen, the above factors are less liable to compromise transfer from blood to alveoli.

Ventilation, perfusion and shunt

In an ideal situation the ventilation delivered to an area of lung would be just sufficient to provide full exchange of oxygen and carbon dioxide with the blood perfusing that area. In the normal setting, whilst neither ventilation (V) nor perfusion (Q) is distributed evenly throughout the lung, their matching is fairly good, with the bases receiving substantially more of both than the apices (Figure 4).

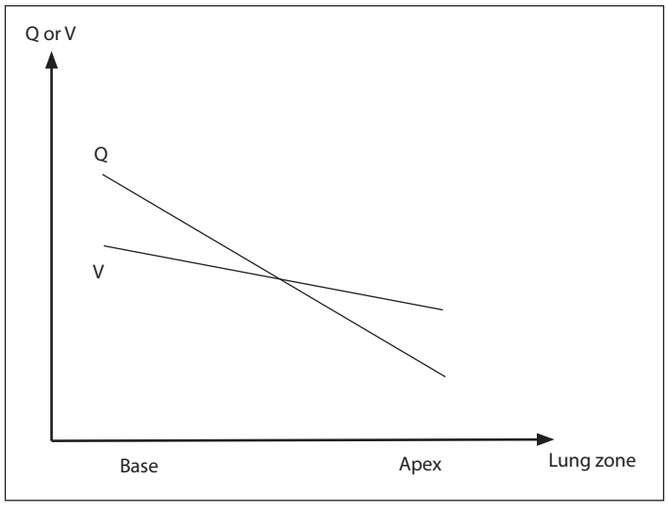

Figure 4. *Distribution of ventilation (V) and perfusion (Q) in the lung*

For **perfusion**, the distribution throughout the lung is largely due to the effects of gravity. Therefore in the upright position this means that the perfusion pressure at the base of the lung is equal to the mean pulmonary artery pressure (15mmHg or 20cmH_2O) plus the hydrostatic pressure between the main pulmonary artery and lung base (approximately 15cmH_2O). At the apices the hydrostatic pressure difference is subtracted from the pulmonary artery pressure with the result that the perfusion pressure is very low, and may at times even fall below the pressure in the alveoli leading to vessel compression and intermittent cessation of blood flow.

The distribution of **ventilation** across the lung is related to the position of each area on the compliance curve at the start of a normal

tidal inspiration (the point of the FRC). Because the bases are on a more favorable part of the compliance curve than the apices, they gain more volume change from the pressure change applied and thus receive a greater degree of ventilation. Although the inequality between bases and apices is less marked for ventilation than for perfusion, overall there is still good **V/Q matching** and efficient oxygenation of blood passing through the lungs.

This traditional explanation of the relationship between ventilation and perfusion has recently been challenged. There is increasing evidence that physiological matching of ventilation and perfusion, despite considerable apparant heterogeneity in both, is achieved by a common pattern of asymmetric branching of the airways and blood vessels.[1]

Disturbance of this distribution can lead to V/Q mismatching (Figure 5). For an area of low V/Q ratio the blood flowing through it will be incompletely oxygenated, leading to a reduction in the oxygen level in arterial blood (hypoxaemia). Providing some ventilation is occurring in an area of low V/Q, the hypoxaemia can normally be corrected by increasing the FiO_2, which restores the alveolar oxygen delivery to a level sufficient to oxygenate the blood fully.

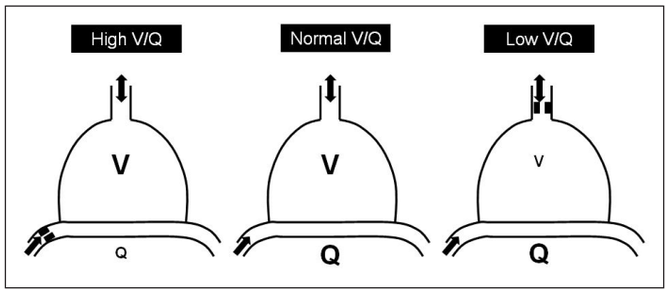

Figure 5. *Ventilation/perfusion (V/Q) mismatch*

V/Q mismatch occurs very commonly during anaesthesia because the FRC falls, leading to a change in the position of the lung on the compliance curve. The apices, therefore, move to the most favorable part of the curve whilst the bases are located on a less favorable part at the bottom of the curve.

At the extremes of V/Q mismatch, an area of lung receiving no perfusion will have a V/Q ratio of ∞ (infinity) and is referred to as **alveolar deadspace**, which together with the anatomical deadspace makes up the physiological deadspace. Ventilating the deadspace is in effect wasted ventilation, but is unavoidable.

In contrast, in an area of lung receiving no ventilation, owing to airway closure or blockage, the V/Q ratio will be zero and the area is designated as **shunt**. Blood will emerge from an area of shunt with a pO_2 unchanged from the venous level (5.3kPa) and produce marked arterial hypoxaemia. This hypoxaemia cannot be corrected by increasing the FiO_2, even to 1.0, as the area of shunt receives no ventilation at all. The well-ventilated parts of the lung cannot compensate for the area of shunt because haemoglobin is fully saturated at a normal pO_2. Increasing the pO_2 of this blood will not increase the oxygen content substantially.

In the case of shunt, therefore, adequate oxygenation can only be re-established by restoring ventilation to these areas using measures such as physiotherapy, PEEP or CPAP, which clear blocked airways and re-inflate areas of collapsed lung. Because closing capacity (CC) increases progressively with age, and is also higher in neonates, these patients are at particular risk during anaesthesia as the FRC may fall below CC causing airway closure.

A physiological mechanism exists which reduces the hypoxaemia resulting from areas of low V/Q ratio, by producing local vasoconstriction in these areas and diverting blood to other, better-ventilated parts of the lung. This effect, known as hypoxic pulmonary vasoconstriction (HPV), is mediated by unknown local factors. The protective action of HPV is, however, inhibited by various drugs, including inhalational anaesthetic agents.

CONTROL OF RESPIRATION

Anaesthesia affects respiratory function in different ways. Knowledge of respiratory physiology is necessary to understand these effects. Physiological control systems involving the nervous system usually have three components. These are:

- A central controlling area
- An afferent pathway
- An efferent pathway.

The neurones (nerve cells) of the controlling area integrate the information from other parts of the body and produce a coordinated response. This response from the central controlling area is carried to the various organs and muscles along efferent pathways. The input to the central controlling area is from the various sensors via the afferent pathways.

Central controlling area

The central controlling area for breathing, called the **respiratory centre**, is in the lower part of the brain stem, in the medulla oblongata. There are "inspiratory neurones" which are active during inspiration and inactive during expiration. Other neurones are active during expiration but not inspiration - the "expiratory neurones". These two groups of neurones automatically maintain a rhythmic cycling pattern of inspiration and expiration. This automatic rhythm can be modified by afferent information.

Afferent supply

Central chemoreceptors

Chemoreceptors are cells that respond to chemical stimuli. There are cells in the floor of the fourth ventricle (part of the brainstem) that respond to the acidity of the cerebrospinal fluid (CSF) and the output from these cells influences breathing. The acidity of any fluid is measured by the pH; this is related to the number of hydrogen ions in the solution.

The normal pH of the body is 7.4, a higher pH than this represents alkaline conditions in the body with a lower hydrogen ion concentration. A pH less than 7.4 represent acidic conditions, with a higher hydrogen ion concentration. The cells in the floor of the fourth ventricle respond to the pH of the CSF. An acidic CSF causes hyperventilation - this is the reason for dyspnoea with conditions such as diabetic ketoacidosis. An alkaline CSF inhibits the respiratory

centre. Carbon dioxide in the blood can rapidly diffuse across into the CSF and there is a balance between the level of carbon dioxide, hydrogen ions and bicarbonate ions in the CSF.

If the carbon dioxide in the blood increases (e.g. following exercise), then the carbon dioxide, hydrogen ion and bicarbonate ion concentrations increase correspondingly in the CSF. This increase in CSF acidity causes hyperventilation which lowers the carbon dioxide concentration in the blood. A low blood carbon dioxide level (hypocarbia) has the opposite effect and may occur, for example, following controlled ventilation during anaesthesia. This may delay the return of spontaneous breathing at the end of surgery.

Peripheral chemoreceptors

The carotid and aortic bodies are small pieces of tissue that contain chemoreceptors which respond to the oxygen and carbon dioxide concentrations in arterial blood. The carotid body is the more important of the two and is situated at the division of the common carotid artery into the external and internal carotid arteries in the neck. The aortic body is found on the aortic arch. The information from the carotid body is carried along the glossopharyngeal nerve (the ninth cranial nerve) and the information from the aortic body is along the vagus nerve (the tenth cranial nerve), to the respiratory centre. The output from the carotid body is thought to provide information to allow immediate regulation of breathing, breath by breath, by the respiratory centre.

In normal people, if the arterial blood reaching the carotid body has a partial pressure of oxygen of 10kPa (80mmHg) or a carbon dioxide partial pressure of more than approximately 5kPa, (40mmHg), then there is an immediate and marked increase in breathing. These limits can be modified by disease or age; for example, people with chronic bronchitis may tolerate an increased concentration of carbon dioxide or a decreased concentration of oxygen in the blood.

Brain

Breathing can be influenced by other parts of the brain. We can all consciously breathe deeply and more rapidly (called hyperventilation), and this can happen, for example, before starting strenuous exercise. Intensely emotional situations, for example, distressing sights, will also cause hyperventilation. Hyperventilation is also part of the response to massive blood loss. This response is co-ordinated by the autonomic system in the hypothalamus and the vasomotor centre in the brain stem.

Lung

There are various receptors in the lung that modify breathing. Receptors in the wall of the bronchi respond to irritant substances and cause coughing, breath holding and sneezing. In the elastic tissues of the lung and the chest wall are receptors that respond to stretch. The exact function of these receptors is not fully understood, but is thought to be responsible for various reflexes that have been discovered in laboratory studies of animals. There are stretch responses that occur when the lung and chest wall are distended and inhibit further inspiration. This is an obvious safety mechanism to avoid overdistension. Conversely, when the lung volume is low, then there are opposite reflexes. A small increase in lung size may stimulate stretch receptors to cause further inspiration. This can sometimes be seen in anaesthetised patients who have been given an opioid; spontaneous breathing may be absent or very slow, but if the patient is given a small positive pressure breath by the anaesthetist, then inspiration is stimulated and the patient takes a deep breath. This reflex may also have some function in newborn babies just after delivery, when small breaths may stimulate further inspiration.

There are also stretch receptors in the blood vessels in the lung. If these are stretched, as in heart failure, the response is to hyperventilate. The information from these receptors in the lung is carried to the respiratory centre along the vagus nerve.

Efferent supply

The efferent nerves from the respiratory centre pass down the spinal cord to the diaphragm, intercostal muscles and accessory muscles of inspiration in the neck. The diaphragm is supplied by the phrenic nerve, that is formed in the neck from the spinal nerves, C3, 4 and 5. The intercostal muscles are supplied by the segmental intercostal nerves that leave the spinal cord between TI and TI2. The accessory muscles in the neck are supplied from the cervical plexus. During normal breathing, inspiration is an active muscular process. Expiration is passive and relies on the natural elasticity of the tissues to deflate the lung. The most important muscle for inspiration is the diaphragm. Any disease that affects the efferent pathways from the respiratory centre to C3, 4 and 5 and then the phrenic nerve to the diaphragm, may cause severe difficulty in breathing. Trauma to the cervical cord, above C3, is normally fatal for this reason.

Anaesthetic drugs and respiration

Opioid drugs, such as morphine or fentanyl, depress the respiratory centre's response to hypercarbia. These effects can be reversed by naloxone. Volatile anaesthetic agents depress the respiratory centre in a similar fashion, although ether has less effect on respiration than the other agents. Volatile agents also alter the pattern of blood flow in the lungs, resulting in increased ventilation/perfusion mismatch and decreasing the efficiency of oxygenation. Nitrous oxide has only minor effects on respiration. The depressant effects of opioids and volatile agents are additive and close monitoring of respiration is necessary when they are combined. When oxygen is not available respiration should always be supported during anaesthesia.

NON-RESPIRATORY LUNG FUNCTIONS

Whilst the main function of the lung is for respiratory gas exchange, it has several other important physiological roles including; a reservoir of blood available for circulatory compensation, a filter for circulating microaggregates, activation of angiotensin II from angiotensin I by angiotensin converting enzyme (ACE), inactivation of several substances such as norepinephrine and bradykinin, and an immunological function by secreting IgA into bronchial mucus.

REFERENCE

1. Galvin I, Drummond GB, Nirmalan M. Distribution of blood flow and ventilation in the lung: gravity is not the only factor. *British Journal of Anaesthesia* (2007); **98**: 420-8.