

## B. 2 Control of Respiration

### a. Describe the medullary and pontine respiratory control centres and explain how the ventilatory pattern is generated and controlled.

There are three main groups of neurones involved in control of respiration, each present bilaterally. In the medulla there is a dorsal respiratory group, mostly in the nucleus of the *tractus solitarius*, which receives sensory input from the vagus and glossopharyngeal nerves. In the ventrolateral part of the medulla is the ventral respiratory group in the *nucleus ambiguus* and *nucleus retroambiguus*. In the superior pons lies the pneumotaxic centre in the *nucleus parabrachialis* and in the lower pons, the apneustic centre.

Inspiration is initiated rhythmically by the dorsal respiratory group, generating periodic bursts of action potentials. This results in an “inspiratory ramp” signal of two seconds of increasing signals to the primary inspiratory muscles. This then ceases for three seconds before the cycle repeats. There are two parameters which vary in the inspiratory ramp signal: its rate of increase, controlling the depth of inspiration and its duration, controlling frequency. Output from the pneumotaxic centre limits the duration of the inspiratory ramp.

When rapid and deep respiration is required, output from the dorsal respiratory group recruits neurones in the ventral respiratory group which generate activity in secondary muscle of respiration, allowing for forceful inspiration and expiration.

The apneustic centre in the lower pons acts to prolong the duration of the inspiratory ramp signal. In the absence of the pneumotaxic centre, it results in sustained inspiration.

Regulation of respiration from breath to breath is maintained by projections of the vagus nerve from stretch receptors in the bronchi and bronchioles which result in ending of the inspiratory ramp signal at tidal volumes over 1.5 l, ending inspiration. This results in the Hering-Breuer inflation reflex.

### b. Describe the chemical control of breathing via central and peripheral chemoreceptors, and indicate how this is altered in abnormal clinical states.

Respiration is responsive to blood  $PO_2$  and  $PCO_2$ . In normal states,  $PCO_2$  plays the major role as it is far more dependent on ventilation.  $CO_2$  diffuses readily across the blood-brain barrier, altering brain and CSF pH in accordance with the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{[HCO_3^-]}{0.03 PCO_2}$$

In the ventral medulla there is a chemosensitive area of neurones which are highly sensitive to  $H^+$  ion concentration in both the interstitial fluid of the brain and particularly the CSF (which is not well-buffered). Stimulation of the chemosensitive area results in stimulation of the inspiratory (dorsal) group, resulting in increased rate of increase of the inspiratory ramp signal and decreased duration, greatly increasing alveolar ventilation (by a factor of 10 over the range of  $PCO_2$  from 40 to 80 mmHg).

The effect on alveolar ventilation of a change in  $PCO_2$ , is of limited duration. Renal compensation for a respiratory acidosis increases  $[HCO_3^-]$  and normalizes pH over a few days, eliminating most of the effect of a rise in  $PCO_2$ .

$PO_2$  plays a role in the control of respiration only in unusual circumstances. Chemoreceptors in the carotid and aortic bodies are directly sensitive to  $PO_2$ , producing a strong response as  $PO_2$  falls below 60 mmHg. They are also sensitive to  $PCO_2$  and pH, but this effect is less than that of the central chemoreceptors. The output of the chemoreceptors in the aortic arch is conducted to the medulla via the vagus nerves and that from the carotid bodies via the glossopharyngeal nerves.

Stimulus from the chemoreceptors results in increased alveolar ventilation via action on the dorsal respiratory group. If gas exchange is normal, the increase in ventilation is considerably damped by the effect of a fall in  $PCO_2$ , however if  $PCO_2$  does not fall or pH is

normalized by renal compensation over a few days, the increase in ventilation is sustained.

### **c. Describe the reflex control of respiration.**

The Hering-Breuer reflex is initiated by pulmonary stretch receptors in the airway smooth muscle. The afferent limb is the vagus nerve. The response is via the medulla, inhibiting inspiratory muscle activity. This reflex is not active in adult humans at rest, but may play a role when tidal volume exceeds 1 litre.

Irritant receptors, or rapidly adapting receptors, are present in the airway epithelium and respond to noxious stimuli such as smoke or dust or cold air. They are innervated by the vagus nerve and result in bronchoconstriction and hyperpnoea.

Juxtacapillary ("J") receptors lie in the alveolar walls close to pulmonary capillaries. They respond to chemicals injected into the pulmonary circulation and conduct impulses via non-myelinated fibres in the vagus to the medulla. Stimulation results in rapid shallow breaths or apnoea. They may play a role in the perception of dyspnoea.

The cough reflex is initiated in response to physical or chemical irritation of receptors in the upper airway, particularly the larynx or carina. The afferent limb is the vagus nerve which projects to the medulla. The reflex is a series of responses of the respiratory centres: inspiration to about half VC, closure of the epiglottis and vocal cords, contraction of the muscles assisting expiration (including rectus abdominis and internal intercostals) to raise intrathoracic pressure to about 100 mmHg and sudden opening of the cords and epiglottis to expel air rapidly through airways partly collapsed by the high intrathoracic pressure. This helps to remove any foreign matter in the airways.

The sneeze reflex is similar except that the afferent limb is the trigeminal nerve from the nasal mucosa and during forceful expiration, the uvula is depressed allowing air to leave through the nose, and the eyes are closed.

In regulation of breathing, the same proprioceptive reflexes operate as in other parts of the body: muscle spindles, Golgi tendon organs and joint receptors.

Breathing control is also affected by responses to stimuli outside the respiratory tract. Pain or sudden cold may result in apnoea followed by hyperventilation. Stimulation of the aortic and carotid body baroreceptors by an increase in blood pressure results in hypoventilation.

### **d. Describe the ventilatory response to exercise.**

With exercise, alveolar ventilation can rise from 5 l/min to over 120 l/min and  $O_2$  use from 0.2 l/min to 4 l/min. These changes parallel the rise in metabolism, maintaining pH,  $PO_2$  and  $PCO_2$  at normal values. The increase in alveolar ventilation starts immediately on starting exercise, resulting from central and possible proprioceptive stimuli rather than following a rise in  $PCO_2$ . Thus the initial change in  $PCO_2$  is a fall, followed by a rise back to normal as increased  $CO_2$  production matches the increased alveolar ventilation. The normal ventilatory response to a change in  $PCO_2$  is superimposed on the response to exercise.

The rise in ventilation on starting exercise is partly a learned response.

### **e. Explain the consequences of altitude on respiratory function.**

Barometric pressure falls with altitude from 760 mmHg at sea level to 349 mmHg at 20000 feet. Inspired  $PO_2$  falls proportionally from 159 to 73 mmHg. Alveolar water vapour pressure remains the same at 47 mmHg and  $P_ACO_2$  remains in the same relationship to  $P_aCO_2$ , further reducing  $P_AO_2$ . At 20000 feet, a person not acclimatized to the altitude will hyperventilate on hypoxic drive to a  $P_aCO_2$  of about 24 mmHg, yielding a  $P_AO_2$  of 40 mmHg, not compatible with normal function.

The respiratory rate at altitude rises because of hypoxic drive. The acute rise is limited by inhibition from a fall in  $P_aCO_2$  and rise in CSF pH. As the pH is normalized over a few days, respiratory rate rises further and  $P_aCO_2$  falls, allowing for a higher  $P_AO_2$  and optimal gas exchange. Levels of 2,3-DPG rise with hypoxia, moving the oxygen-haemoglobin

dissociation curve to the right. This opposes the left shift due to alkalaemia and reduced  $P_a\text{CO}_2$ . Over a longer period, haematocrit rises (up to 200 g/l), blood volume increases, tissue vascularity increases and cellular oxygen useage improves, providing further compensation for hypoxia.

Acute complications of high altitude are: hypoxia with accompanying cerebral dysfunction, acute cerebral oedema due to vasodilatation resulting from hypoxia and acute pulmonary oedema of uncertain mechanism.

Long term complications are termed Chronic Mountain Sickness: a rise in haematocrit and pulmonary vasoconstriction leads to pulmonary hypertension and falling blood flow and oxygen transport as well as shunting through non-alveolar pulmonary vessels. High pulmonary pressure and poor oxygenation results in right heart failure with secondary biventricular failure. Treatment is by oxygen supplementation, generally by moving to a lower altitude.

In an acclimatized person at 20000 feet,  $\text{PACO}_2$  falls to 10 mmHg and  $\text{PAO}_2$  rises to 53 mmHg, allowing for an oxygen saturation of 85%.

#### **f. Explain the consequences of pregnancy on respiratory control.**

in [Maternal Physiology \(1.0\)](#)

#### **g. Describe and explain the effects of anaesthesia on respiratory control.**

Anaesthesia affects the  $\text{CO}_2$  response curve by flattening the curve and raising the  $\text{PCO}_2$  which will be tolerated in apnoea. In an individual patient, ventilation falls as the level of inhalational agent rises, coming to equilibrium at a higher  $\text{PCO}_2$  and lower minute volume. Apnoea cannot be sustained on spontaneous ventilation of inhalational agent alone.

Induction and preinduction agents, especially narcotics, flatten the  $\text{CO}_2$  response further, surgical stimulus antagonizes it. The inhalational agents all display similar degrees of respiratory depression for a given depth of anaesthesia, but diethyl ether produces less depression up to 2.5 MAC.

The hypoxic ventilatory response is extremely sensitive to inhalational agents, being markedly blunted at 0.1 MAC, and abolished at 1.1 MAC. This is thought to be through action at the carotid body chemoreceptors. This effect necessitates continuous  $\text{SaO}_2$  monitoring in anaesthesia and is particularly dangerous for patients reliant on hypoxic drive: those with severe COAD.

The ventilatory response to metabolic acidosis is reduced as much as that to hypoxia.

Breathing reflexes remain intact in spontaneously ventilated anaesthesia. Increased force of inspiration in the face of resistance is a muscle spindle reflex which is unchanged. Increasing resting volume in response to expiratory obstruction is also preserved. The Hering-Breuer response remains unimportant under anaesthesia.

The mechanics of breathing are affected by anaesthesia. Movement from the intercostals is reduced far more than diaphragmatic movement, producing "abdominal breathing". The resting position of the diaphragm is higher in the thorax than when awake, reducing FRC. These are partially compensated for by a movement of blood from thorax to abdomen in the supine position in anaesthesia, but FRC remains reduced by about 450 ml. Paralysis does not alter FRC further.

Whether the reduction in FRC is accompanied by a fall in closing volume is uncertain. Airway calibre is reduced at lower FRC, but the increase in resistance which is expected from this is offset by the bronchodilator effect of inhalational agents. The anaesthetic circuit introduces additional resistance to breathing, particularly with small ET tubes, resistance varying inversely with greater than the fourth power of radius for turbulent flow. Without assistance, upper airway resistance is frequently very high due to obstruction by the tongue.

Compliance is reduced almost immediately upon induction of anaesthesia. The cause of this is uncertain, but the change is in pulmonary compliance, not in the chest wall. It may be due to interference with the activity of surfactant or pulmonary collapse due to the

reduction in FRC.

Metabolic rate is reduced a little by anaesthesia, particularly cerebral and cardiac oxygen consumption.

Gas exchange is impaired in anaesthesia because of the fall in minute volume in spontaneous ventilation, and because of the increase in V/Q scatter which is an unavoidable consequence of anaesthesia. The increased V/Q scatter is manifest in calculations of physiological dead space and shunt.

There is little rise in physiological dead space in spontaneous ventilation, but with paralysis, physiological dead space increases measurably. The increase occurs in alveolar dead space, anatomical dead space remaining unchanged. Alveolar ventilation is normally well-maintained as minute ventilation is increased to keep PCO<sub>2</sub> stable. The mechanism for the increase in dead space is thought to be maldistribution of ventilation.

Physiological shunt increases with anaesthesia from about 1-2% in healthy individuals to about 10%. This results in a substantial increase in A-a gradient. This effect is most marked in older patients and less in young adults. The cause of the increase in shunt may be impairment of the hypoxic vasoconstrictor response as well as maldistribution of ventilation or localized pulmonary collapse. The last possibility seems unlikely given the lack of benefit from PEEP in anaesthesia. PEEP may have some effect in improving ventilation, but it also reduces cardiac output, negating any improvement in oxygen flux.