Respiratory failure occurs when pulmonary gas exchange is sufficiently impaired to cause hypoxaemia (conventionally $P_aO_2 < 8$ kPa or 60 mmHg) with or without hypercarbia (conventionally $P_aCO_2 > 7$ kPa or 55 mmHg).

The respiratory system consists of a gas-exchanging organ (the lungs) and a ventilatory pump (respiratory muscles/thorax), either or both of which can fail and precipitate respiratory failure.

**ACUTE HYPOXAEMIC (TYPE I) RESPIRATORY FAILURE**

Acute hypoxaemic (type I) respiratory failure (ARF) is caused by diseases that interfere with gas exchange by damaging lung tissue. Hypoxaemia is due to right-to-left shunts, ventilation/perfusion ($V/Q$) mismatch or, most often, a combination of these two. As discussed in Chapter 3, barriers to diffusion are almost never an important cause of hypoxaemia. An increase in right-to-left shunt occurs when alveoli are completely collapsed, become totally consolidated or are filled with oedema fluid. $V/Q$ inequalities result from pulmonary parenchymal disease that causes regional variations in compliance, an increased scatter of time constants (see Chapter 3) and/or abnormalities of perfusion. Also, functional residual capacity (FRC) is reduced so that tidal exchange takes place below closing volume (i.e. airway closure is present throughout the respiratory cycle), an abnormality that is associated with an increase in the number of relatively underventilated lung units.

Initially, there is usually an increase in total ventilation, which compensates for the increased dead space ($V_D$) and maintains $P_aCO_2$ at normal levels. Indeed, relative hyperventilation, possibly in response to severe hypoxaemia and/or stimulation of irritant and mechanoreceptors within the lungs, may cause a reduction in $P_aCO_2$. The degree of hypoxaemia is limited by constriction of vessels supplying those alveoli with a low $PO_2$ – hypoxic pulmonary vasoconstriction – although the intensity of this response is very variable and appears to be genetically determined (see Chapter 3).

As well as the impairment of gas-exchanging properties, the lungs deteriorate mechanically with a reduction in compliance (associated with the fall in FRC; see Chapter 3) and/or an increase in resistance, so that the work and metabolic cost of breathing are increased. Under these circumstances, patients find it easier to breathe rapidly with a low tidal volume ($V_T$). Finally, these patients are often pyrexial, with a raised metabolic rate, and this further increases both oxygen consumption ($VO_2$) and the volume of carbon dioxide that has to be excreted. Therefore the characteristic clinical features of ARF include:

- hypoxia;
- hypocarbia;
- tachypnoea;
- small $V_T$.

In contrast to the normal pattern of ventilation, there is little moment-to-moment variation in either respiratory rate or $V_T$.

**VENTILATORY (TYPE II) RESPIRATORY FAILURE**

Ventilatory failure occurs when alveolar ventilation is insufficient to excrete the volume of carbon dioxide being produced by tissue metabolism. Carbon dioxide is therefore retained, producing an increase in both arterial and alveolar $PCO_2$. Due to the operation of the alveolar gas equation (see Chapter 3, equation 3.16), this inevitably leads to a fall in alveolar oxygen tension ($P_aO_2$) and, when breathing air, hypoxaemia, even in patients with normal lungs. Inadequate alveolar ventilation may be due to:

- reduced ventilatory effort;
- inability to overcome an increased resistance to ventilation;
- failure to compensate for an increase in $V_D$ and/or carbon dioxide production;
- a combination of these factors.

The respiratory muscles have a large reserve, however, and considerable impairment of function may be present without...
ventilatory failure. Characteristic clinical features of pure ventilatory failure, therefore, include:

- hypercarbia;
- hypoxia;
- a reduced rate and/or depth of breathing.

These patients may suffer from an extremely distressing sensation of breathlessness, even when ventilation is apparently adequate (e.g. judged by blood gas values).

MIXED RESPIRATORY FAILURE

Often, the two types of respiratory failure are combined to produce a mixed picture. As discussed above, acute diseases of the pulmonary parenchyma initially cause purely hypoxaemic respiratory failure. In some cases, however, exhaustion eventually supervenes; the patient is then unable to overcome the mechanical impairment of lung function and cannot compensate for the increased V′, and carbon dioxide production. At this stage, the P′CO₂ begins to rise, leading to a picture of mixed respiratory failure.

Ventilatory failure is often complicated by the subsequent development of pulmonary abnormalities. This is because these patients are unable to cough effectively, sigh or take deep breaths, and are therefore at risk of alveolar collapse, retention of secretions and secondary infection. In those with an associated bulbar palsy, aspiration can occur and further damage the lungs.

RESPIRATORY MUSCLE DYSFUNCTION

Respiratory muscle fatigue (see Chapter 3) has been demonstrated in healthy subjects submitted to high inspiratory resistive loads and may also play a role in the development of respiratory failure, although overt respiratory muscle fatigue is probably unusual and the underlying mechanisms are not yet fully understood. Increased ‘fatigability’, of the sternomastoid muscle has, however, been demonstrated in patients with severe respiratory disease on admission to hospital (Efthimiou et al., 1987), and this appeared to resolve as the patient recovered. It was suggested that respiratory muscle fatigue had contributed to hypercapnia in these patients, although the exact significance of these findings remains unclear. It has also been postulated that chronic respiratory muscle fatigue, a poorly understood phenomenon, may contribute to the development of hypercapnia in chronic respiratory failure.

Predisposing factors to the development of respiratory muscle fatigue include:

- an increased load (e.g. imposed by airways obstruction, a reduction in lung compliance or chest wall abnormalities);
- muscle weakness related to neuromuscular disorders (see Chapters 3 and 15), disuse atrophy, malnutrition, generalized wasting or old age.

Muscle dysfunction may be exacerbated by:

- sepsis;
- metabolic disturbances;
- hypoxaemia;
- hypercarbia;
- hyperinflation (see later).

In addition, profound reductions in respiratory muscle blood flow, such as may occur in cardiogenic shock, can lead to impaired respiratory muscle contraction in the face of increased excitation, especially when combined with the increased demands imposed by compensatory hyperventilation and pulmonary oedema (Aubier et al., 1981).

Mechanisms that may mediate fatigue include:

- inhibition of neural drive;
- impaired neuromuscular transmission;
- excessive force and duration of contraction;
- impaired excitation–contraction coupling;
- depletion of muscle energy stores;
- failure of the contractile machinery.

Two types of muscle fatigue can be identified:

- high-frequency fatigue, which is thought to be due to impaired neuromuscular transmission and/or propagation of the action potential;
- low-frequency fatigue, which may reflect impaired excitation–contraction coupling.

Although high-frequency nerve stimulation generates maximum muscle tension, the force of contraction rapidly falls when it persists. If this high-frequency fatigue were allowed to develop in the respiratory muscles there would be a rapid and catastrophic loss of ventilatory capacity. Lower-frequency stimulation produces less initial force, but tension is well maintained and soon exceeds that generated by high-frequency stimulation. Low-frequency fatigue of respiratory muscles, which experimentally is long-lasting and associated with muscle fibre damage, may be an important component of ventilatory failure, but is only precipitated by massive overload and has proved difficult to demonstrate clinically. It may be that neither low-frequency fatigue, with muscle damage, nor high-frequency fatigue, with the rapid onset of extreme respiratory failure, occurs readily because the central nervous system will not (or cannot) drive the peripheral contractile apparatus sufficiently hard (Moxham, 1990). Moreover, in patients with congestive cardiac failure or severe chronic obstructive pulmonary disease (COPD) the proportion of slow-twitch fibres decreases, an adaptation which may increase the resistance of the diaphragm to fatigue and is probably a response to constant moderate exercise (Levine et al., 1997). Interestingly, in one study patients with COPD did not develop low-frequency diaphragmatic fatigue when exercised to exhaustion (Polkey et al., 1995).

The role of central fatigue in respiratory failure is uncertain, but it may be that respiratory drive is modified to avoid not only central, but also high-frequency and low-frequency fatigue and thereby optimize ventilation, albeit at the cost of
hypercapnia. Ventilatory failure may therefore be the result of a reduction in central drive, which is intended to protect the respiratory muscles from overload and fatigue. For example, during weaning from mechanical ventilation, if the load is excessive and unsustainable, patients breathe rapidly with a low $V_t$. This reduces the work of breathing, but at the expense of carbon dioxide retention.

**Clinical features of respiratory muscle fatigue**

It has been suggested that tachypnoea, asynchronous or paradoxical respiration, respiratory alternans and eventually a rising $P_{aCO_2}$ with a reduction in respiratory rate and minute volume are indicative of respiratory muscle fatigue. In *asynchronous respiration* there is a discrepancy in the rate of movement of the thoracic and abdominal compartments, while in *paradoxical respiration* they move in opposite directions. *Respiratory alternans* is caused by recruitment and derecruitment of the accessory/intercostal muscles and the diaphragm, leading to an increase in the breath-to-breath variation in the relative contribution of the ribcage and abdomen to $V_t$.

At present, however, there is no convincing evidence that any particular constellation of physical signs can serve as a sensitive or specific marker of respiratory muscle fatigue. The detection of an abnormal pattern of thoracoabdominal motion does, however, suggest a significantly increased respiratory load. Objective measures of respiratory muscle strength and fatigue are discussed in Chapter 7.

**CAUSES OF RESPIRATORY FAILURE**

Respiratory failure is commonly precipitated by:

- surgical operations (particularly upper abdominal or thoracic);
- acute respiratory tract infections;
- the administration of depressant drugs.

The causes of respiratory failure can best be considered according to anatomical location (Fig. 8.1).

**RESPIRATORY CENTRE**

Causes of depression of the respiratory centre commonly seen in the intensive care unit (ICU) include:

- raised intracranial pressure or direct trauma (e.g. head injury);
- infections (e.g. meningoencephalitis);
- vascular lesions;
- drug overdose (e.g. narcotics, barbiturates).

Patients in traumatic coma with intracranial hypertension may also have associated pulmonary oedema, lung contusion or aspiration pneumonia. Frequently, the laryngeal reflexes are also depressed and in some cases there may be a true bulbar palsy. Both predispose the patient to aspiration pneumonitis. Severe hypoxia and extreme hypercarbia can also reduce the responsiveness of the respiratory centre.

**Sleep-related respiratory disturbances**

**CENTRAL SLEEP APNOEA**

In central sleep apnoea, there is periodic cessation of spontaneous impulse formation during sleep, which leads to repeated episodes of apnoea with absent respiratory efforts.

Complaints of dyspnoea and other respiratory findings are rarely prominent. Patients may present with:

- lethargy;
- headache;
- daytime sleepiness;
- unexplained polycythaemia;
- pulmonary hypertension;
- cor pulmonale.

Patients with *primary alveolar hypoventilation*, in whom there is a blunted ventilatory response to hypoxia and hypercarbia in the absence of abnormal lung function, may present with similar signs and symptoms. An example is the *Pickwickian syndrome* in which hypoventilation occurs in very
obese, somnolent men who are said to resemble the fat boy, Joe, in Charles Dickens’ The Pickwick Papers.

OBSURCTIVE SLEEP APNOEA

Patients with obstructive sleep apnoea suffer from intermittent functional upper-airway obstruction during sleep, which is thought to be due to episodic loss of pharyngeal tone. This is associated with loud snoring, frequent apnoeic episodes, especially during rapid-eye movement (REM) sleep, with severe hypoxaemia and repeated nocturnal awakening or arousal. Although traditionally associated with obesity, many patients are not significantly overweight. The condition is also associated with COPD and a reduced size of the pharyngeal opening, even when the patient is awake.

Occasionally obstructive sleep apnoea is associated with:

- daytime hypersomnolence;
- poor concentration;
- morning headache;
- impotence;
- systemic/pulmonary hypertension;
- unexplained cor pulmonale;
- polycythaemia.

The diagnosis is made when a sleep study demonstrates frequent severe apnoeic episodes associated with marked oxygen desaturation and vigorous respiratory efforts.

Correctable factors include:

- encroachment on the pharynx (obesity, acromegaly, enlarged tonsils);
- nasal obstruction (nasal deformities, rhinitis, polyps, adenoids);
- respiratory-depressant drugs (alcohol, sedatives, strong analgesics).

SPINAL CORD

Very rarely, lesions of the high cervical cord or brainstem may interrupt the pathways involved in automatic breathing, while leaving the conscious pathways intact. Because these unfortunate patients have to remember to breathe, there are long periods of apnoea, even when the subject is awake, and serious carbon dioxide retention develops when they fall asleep. The hypercarbia increases cerebral blood flow, causing headaches, nightmares and distressed sleep patterns. This condition has been called Ondine’s curse, after a water nymph who, according to German mythology, cursed her husband by abolishing all his automatic functions. When he finally became exhausted and fell asleep, he died.

Traumatic damage to the spinal cord at or above the origin of the phrenic nerve (C3, C4, C5) causes severe ventilatory failure since only the accessory muscles are spared. Partial lesions are common, while cord damage below this level causes less severe respiratory impairment since diaphragmatic breathing remains intact (see Chapter 10).

Poliomyelitis has its major impact on the anterior horn cells in the spinal cord and/or the motor nuclei of the cranial nerves and, in some cases, the respiratory centre itself is involved. The patient may therefore have a bulbar paralysis, in which case airway protection is vital, or spinal polio, which may cause weakness of the respiratory muscles and ventilatory failure. Sometimes both bulbar and spinal motor nuclei are affected.

If the spasms of tetanus are prolonged and severe, they may interfere with ventilation, but in any case treatment of the most severe cases consists of heavy sedation, paralysis and artificial ventilation (see Chapter 15). There is also some evidence that tetanus causes respiratory depression by a direct effect on the brainstem.

Motor neurone disease is a progressive disorder affecting the cerebral cortex, brainstem and spinal cord and is manifested as muscular atrophy with spasticity and hyperreflexia. It is a disease of middle age, which usually progresses inexorably and relatively rapidly (2–5 years) until, in the absence of intervention, death supervenes from respiratory failure, often associated with aspiration pneumonia. There is no known treatment but a nihilistic approach to ventilatory support is no longer tenable. Non-invasive ventilation may improve survival and quality of life in some patients, symptoms of nocturnal hyperventilation and dyspnoea can often be controlled and the need for tracheostomy/invasive ventilation may be obviated (Simonds, 2000). Nevertheless the decision to institute respiratory support in such cases is often far from straightforward. The participation of the patient, family and carers in decision-making is therefore essential (see Chapter 2).

MOTOR NERVES

In Guillain–Barré syndrome, lower motor neurone weakness develops a few days, or even weeks, after a flu-like illness. Usually the lower limbs are affected first, but later weakness may spread to the muscles of the face and trunk. A significant proportion of patients with this syndrome then develop ventilatory failure and require ventilatory support (see Chapter 15).

NEUROMUSCULAR JUNCTION

Although myasthenia gravis may affect any voluntary muscle, ventilatory failure is unusual except during acute exacerbations (myasthenic crisis), overdosage with anticholinesterases (cholinergic crisis) or postoperatively (following thymectomy) (see Chapter 15).

Botulism is an extremely rare form of food poisoning in which botulinum toxin prevents the release of acetylcholine from motor nerve endings, causing flaccid paralysis and ventilatory failure.

Organophosphorous compounds have been developed as chemical weapons and are used as insecticides. They are long-acting anticholinesterases and produce respiratory depression, bronchospasm, salivation, bradycardia, hypertension and convulsions (see Chapter 19).

Failure to reverse the effects of neuromuscular-blocking agents used during anaesthesia is an occasional cause of
admission to intensive care and high-dependency units for mechanical ventilation.

**CHEST WALL**

If a segment of chest wall becomes unstable (e.g. due to multiple rib fractures), particularly when associated with lung contusion, it may be impossible to sustain adequate ventilation (see Chapter 10). Similarly, if the thorax is deformed (e.g. due to kyphoscoliosis), lung expansion will be impaired. These patients may eventually develop ventilatory failure and are prone to recurrent chest infections. On the other hand, ventilatory failure is unusual when chest movement is restricted, but the thorax is uniform (e.g. as in ankylosing spondylitis).

Rarely, patients with myopathies or myositis may develop respiratory failure. Mechanical ventilation may be required and can allow time for the diagnosis to be established (e.g. by muscle biopsy).

**PLEURA**

*Pneumothorax, haemothorax, pleural effusion and empyema* may all cause or exacerbate respiratory failure.

**LUNGS AND AIRWAYS**

As discussed above, diseases affecting primarily the lungs and airways initially cause hypoxaemic respiratory failure, but may later progress to the mixed type. Causes of ARF include pneumonia, asthma, left ventricular failure, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (see below). Examples of chronic type I respiratory failure include emphysema and fibrosing lung disease. The commonest cause of mixed respiratory failure is COPD. Upper-airway obstruction is usually well tolerated initially, but can rapidly progress to frank respiratory failure.

**PULMONARY CIRCULATION**

As well as mechanically obstructing the circulation (see Chapter 5), acute pulmonary embolism can cause V/Q inequalities, possibly via reflex mechanisms, with hypoxaemia and tachypnoea. Recurrent pulmonary emboli eventually produce chronic pulmonary hypertension and respiratory failure.

**PRINCIPLES OF MANAGEMENT**

Clearly, the specific treatment of respiratory failure will vary according to the underlying cause, but the same general principles apply in all cases:

- Hypoxaemia should be corrected.
- The load on the respiratory muscles should be reduced by improving lung mechanics and controlling fever.
- Ventilatory pump capacity should be optimized.

Specific measures include:

- administration of supplemental oxygen;
- control of secretions;
- treatment of pulmonary infection;
- treatment of airways obstruction;
- measures to limit pulmonary oedema;
- mechanical respiratory support.

The importance of chest wall stiffness and decreased abdominal compliance in increasing the respiratory load is sometimes not fully appreciated. Since it seems unlikely that overt high- or low-frequency fatigue is allowed to develop in respiratory failure, specific therapy to counteract fatigue is probably of little value (Moxham, 1990).

Respiratory failure must not be considered in isolation. Not only do hypoxia and hypercarbia adversely affect cardiovascular performance, but a low cardiac output is associated with a reduction in \( P_{O_2} \), exacerbating the adverse effect of a given degree of shunt on arterial oxygenation. Low cardiac output is also associated with a decrease in respiratory muscle blood flow, anaerobic metabolism in respiratory muscles (which exacerbates lactic acidosis) and respiratory muscle fatigue (Aubier et al., 1982). Many drugs that act on the cardiovascular system, such as dopamine and glyceryl trinitrate, have been shown to increase pulmonary venous admixture, probably by reversing hypoxic pulmonary vasoconstriction. Myocardial failure often causes pulmonary congestion with increased shunting, and hypotension may lead to an increased dead space, particularly during positive-pressure ventilation. Finally, the increased work and metabolic cost of breathing increase the load on the myocardium and respiratory system.

**OXYGEN THERAPY**

*Indications*

Supplemental oxygen is always indicated in patients with acute hypoxaemic or mixed respiratory failure. For reasons discussed previously, oxygen therapy is most effective when the main abnormality is V/Q mismatch, but is less efficacious in the presence of a fixed right-to-left shunt (see Chapter 3).

In patients with pure ventilatory failure, the primary abnormality is retention of carbon dioxide; specific treatment is therefore directed towards lowering \( P_{CO_2} \) and \( P_{A}CO_2 \). The administration of oxygen is, however, a useful first step since it effectively reverses the hypoxia caused by the elevated \( P_{A}CO_2 \).

Patients with carbon monoxide poisoning will also benefit from oxygen administration. By increasing \( P_{O_2} \), the dissociation of carboxyhaemoglobin is accelerated and the increase in dissolved oxygen improves tissue oxygenation (see Chapters 3 and 19).

*Methods of oxygen administration*

In mechanically ventilated patients, the inspired oxygen concentration \( (F_{O_2}) \) is easily measured (see Chapter 3) and can be maintained at the desired level by mixing air and oxygen.
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