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collapse when worn during sleep. These devices reduce snoring, AHI and nocturnal oxygen desaturation and reduce objective and subjective sleepiness in patients with OSA, though not as effectively as CPAP. Not all patients respond to mandibular advancement devices. Short-term side-effects include temporomandibular joint discomfort and excess salivation. Occlusal changes may occur with long-term use, and regular dental reviews are recommended. Mandibular advancement devices probably have a role in patients who cannot or will not use CPAP, and in those with mild disease. Specialist orthodontic collaboration is recommended for appropriate prescription.

Drugs are generally unhelpful in OSAS. Tricyclic antidepressants (e.g. protriptyline) reduce REM sleep time and so may improve OSAS in patients with REM-predominant disease. However, anticholinergic side-effects limit their use, particularly in men.

Surgery - nasal surgery is seldom useful in OSAS. Surgery can be curative in OSAS in children and adolescents with adenotonsillar hypertrophy; adults may derive some benefit, but cure is rare. The postoperative period may be hazardous if OSA is untreated. Uvulopalatopharyngoplasty involves removal of the tonsils, the uvula and parts of the soft palate and pharyngeal folds. It is the most commonly performed surgical procedure in OSAS, but carries significant morbidity, and an AHI of less than 20 is achieved in fewer than 50% of patients. There are no reliable means of improving patient selection, and subsequent use of CPAP may be more difficult. Laser-assisted and radiofrequency ablation palatal procedures are not effective in the treatment of OSA.

Complex maxillofacial surgery may be effective in OSAS when performed by experienced groups; success rates of more than 90% have been reported. The procedure is performed in two stages – genioglossal advancement via a mandibular osteotomy, with uvulopalatopharyngoplasty and nasal surgery, followed by maxillomandibular osteotomy and advancement. There is significant associated morbidity, however, and the procedure is not widely available.

Tracheostomy is usually required only as a last resort in patients with severe or complicated OSAS who are unable to tolerate CPAP. It is effective, but carries significant morbidity, particularly in obese patients.

**FURTHER READING**

Malhotra A, White D P. Obstructive sleep apnoea. *Lancet* 2002; 360: 237–45.

Young T, Peppard P E, Gottlieb D J. State of the art – epidemiology of obstructive sleep apnea. *Am J Resp Crit Care Med* 2002; 165: 1217–39.

*(An excellent discussion of adverse cardiovascular outcomes.)*

**Practice points**

- OSAS is common and significantly affects daytime functioning
- OSAS is not confined to patients with obesity
- CPAP is the most effective available treatment for OSA
- OSA is an independent risk factor for hypertension and other cardiovascular diseases, including coronary artery disease, stroke and congestive cardiac failure

### Respiratory failure

Christopher B Cooper

The respiratory system has two principal purposes – to maintain adequate arterial PaO₂, and to regulate arterial PaCO₂, and thereby maintain a stable acid–base state. Both are necessary to sustain normal tissue metabolism. Respiratory failure can be defined in two ways:

- **failure of oxygenation**, resulting in PaO₂ < 8.0 kPa
- **failure of ventilation**, resulting in PaCO₂ > 6.7 kPa with accompanying acid–base changes.

**Failure of oxygenation** – the definition of respiratory failure takes account of the sigmoidal oxyhaemoglobin dissociation curve (Figure 1) and recognizes that significant decreases in haemoglobin saturation (and thus arterial oxygen content) do not occur until PaO₂ is less than 8.0 kPa (Sao₂ 90%). Oxygenation failure can result from poor alveolar ventilation, diffusion abnormality, ventilation/perfusion mismatch and/or shunt. When the cause is diffusion abnormality, ventilation/perfusion mismatch or shunt, and the individual can increase alveolar ventilation in response to hypoxaemia, PaCO₂ is reduced and pH increased.

**Failure of ventilation** – regulation of PaCO₂ depends on maintenance of adequate alveolar ventilation. There is a hyperbolic relationship between PaCO₂ and alveolar ventilation, depending on the metabolic rate (Figure 2). Hence, as alveolar ventilation decreases, PaCO₂ increases and vice versa. At rest, alveolar ventilation must be about 4.5 litres/minute to regulate PaCO₂ to 5.3 kPa.

Assuming that the arterial and alveolar partial pressures of carbon dioxide are equal:

$$\text{PacO}_2 \ (\text{kPa}) = \frac{115 \cdot \text{VCO}_2}{\text{VA}}$$

where VCO₂ is metabolic carbon dioxide production in litres per minute at standard temperature and pressure, dry, and VA is alveolar ventilation in litres per minute at body temperature and pressure, saturated with water vapour.

According to the definition of respiratory failure, alveolar ventilation must decrease by about 20%, resulting in an increase in PacO₂ from 5.3 kPa to 6.7 kPa. If acute, such a change would result in acute respiratory acidosis with a decrease in pH from 7.40 to 7.30 (see below). When failure of ventilation results in failure of
oxygenation, the decrease in $P_{aO_2}$ corresponds closely with the increase in $P_{aCO_2}$, depending on the respiratory exchange ratio.

**Causes**

- Airway obstruction (Figure 3) limits airflow and thereby reduces alveolar ventilation. Upper airway problems are usually acute (except obstructive sleep apnoea, which causes repetitive episodes of nocturnal hypventilation and leads to chronic pathophysiological changes). Lower airway problems tend to be chronic; exacerbations cause ventilation/perfusion mismatch and hypventilation as a result of the increased work of breathing.
- Disorders of the lung parenchyma impair gas exchange ability as a result of diffusion abnormalities or ventilation/perfusion mismatch, and tend to increase the work of breathing because of reduced lung compliance.
- Disorders of the respiratory muscle pump lead to alveolar hypoventilation.

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**Pathophysiology**

**Failure of oxygenation**

Acute hypoxaemia reduces arterial oxygen content as determined by the oxyhaemoglobin dissociation curve (Figure 1). Acute hypoxaemia can be life-threatening and is associated with loss of consciousness; if it is severe or prolonged, severe irreversible hypoxic encephalopathy occurs. It also causes pulmonary vasconstriction with a modest increase in pulmonary artery pressure, and renal vasconstriction with secondary effects on renal function. At $P_{aO_2}$ less than 8.0 kPa, carotid body stimulation increases respiratory drive. Unless the cause is alveolar hypventilation, ventilation increases, causing $P_{aO_2}$ to increase and $P_{aCO_2}$ to decrease.

Chronic hypoxaemia has important pathophysiological consequences (polycythaemia, pulmonary hypertension and cor pulmonale). Hypoxaemia stimulates renal secretion of erythropoietin, increasing RBC production. Raised haematocrit increases the oxygen-carrying capacity of the blood (tends to compensate for reduced haemoglobin saturation associated with hypoxaemia) and increases blood viscosity (compromising tissue blood flow such that venesecion should be considered when haematocrit > 55%). Chronic hypoxaemia has adverse consequences in the pulmonary circulation. Pulmonary arterioles and precapillary vessels are remodelled by deposition of longitudinal muscle fibres in the intima of the vessels, and vessel narrowing increases pulmonary vascular resistance, leading to modestly increased pulmonary artery pressure. Increased afterload in the pulmonary circulation eventually leads to right ventricular hypertrophy, which defines cor pulmonale. The association between cor pulmonale and peripheral oedema cannot be explained by simple haemodynamic means. The mechanisms are not fully understood.

**Failure of ventilation**

Acute failure results in respiratory acidosis with increased $P_{aCO_2}$ and a decrease in $P_{aO_2}$ in pH. The reduced pH can lead to life-threatening cardiac dysrhythmias, most commonly multifocal atrial tachycardia. Hypercapnia causes vasodilatation, which accounts for some of the clinical manifestations of acute ventilatory failure.

Chronic failure with prolonged hypercapnic respiratory acidosis leads to metabolic compensation by renal retention of bicarbonate; thus, pH tends to return towards normal. This adaptive mechanism develops over several days and is probably complete in about 2 weeks. Patients can tolerate chronic severe hypercapnia with a relatively normal acid–base state, but are at risk of worsening respiratory acidosis in acute exacerbations of chronic failure.

**Interpretation of arterial blood gases**

Hypoxaemia – normal $P_{aO_2}$ when breathing room air at sea level declines with age, from about 13.3 kPa in childhood to about 9.3 kPa in the elderly, because of a subtle deterioration in gas exchange efficiency, leading to an increasing alveolar–arterial oxygen gradient ($P_{aO_2}$ $- P_{aO_2}$). Calculation of $P_{aO_2}$ $- P_{aO_2}$ allows hypoxaemia caused by alveolar hypventilation or altitude to be distinguished from other mechanisms such as diffusion impairment, ventilation/perfusion mismatch and shunt. Assuming normal $P_{aCO_2}$, $P_{aO_2}$ when breathing room air at sea level is about 13.3 kPa.
RESPIRATORY FAILURE

\[ \text{PAO}_2 = (P_b - 6.3) \times 0.21 - \text{Paco}_2 \]

where \( P_b \) is the barometric pressure in kPa, 6.3 is the partial pressure of water vapour in the alveolar compartment at normal body temperature, 0.21 is the fractional concentration of oxygen in room air and \( R \) is the respiratory exchange ratio.

At sea level breathing room air, \( \text{PAO}_2 = 20 - (5.3/0.8) = 13.3 \text{ kPa} \). The normal alveolar–arterial oxygen gradient can be predicted from \( \text{PAO}_2 - \text{Pao}_2 = (0.044 \times \text{age}) - 0.3 \text{ kPa} \).

\( \text{PAO}_2 - \text{Pao}_2 \) is increased when hypoxaemia is caused by diffusion impairment, ventilation/perfusion mismatch or shunt.

It is not unusual for hypoxaemia to stimulate ventilation of relatively normal areas of lung, reducing \( \text{Paco}_2 \), but when hypoxaemia is caused purely by alveolar hypoventilation, \( \text{PAO}_2 \) is decreased and \( \text{PAO}_2 \) increased, and \( \text{PAO}_2 - \text{Pao}_2 \) should be normal.

(For example, a patient suffering opiate intoxication presents with pH 7.10, \( \text{Paco}_2 \) 10.7 kPa and \( \text{Pao}_2 \) 6.0 kPa breathing room air. \( \text{PAO}_2 \) is 6.7 kPa and \( \text{PAO}_2 - \text{Pao}_2 \) is only 0.67 kPa.)

\textbf{Acid–base state} – pH indicates whether there is a tendency towards acidity (acidosis) or alkalinity (alkalosis). \( \text{Paco}_2 \) can be easily assessed to see if the change in this could account for the
pH change. If it does, respiratory disturbance is present. In the acute setting, every 0.13 kPa increase in PaCO₂ is associated with a 0.01 decrease in pH. A further simple estimate can be used to assess whether the acid–base disturbance is acute or more complex.

In acute metabolic disturbances, every 0.5 mmol/litre change in bicarbonate is associated with a 0.01 change in pH.

\[ \text{pH (} \Delta \text{0.01)} \propto \text{HCO}_3^- (\Delta \text{0.5 mmol/litre})/\text{PaCO}_2 (\Delta \text{0.13 kPa}) \]

(This is a modified Henderson–Hasselbalch equation showing changes that would be equivalent in a patient with acute respiratory or metabolic disturbance.)

In a patient with pH 7.34 and PaCO₂ 8.0 kPa:
- there is an acidosis
- PaCO₂ could account for it
- an acute increase in PaCO₂ of 2.7 kPa would reduce pH by 0.2, from 7.40 to 7.20.

The fact that pH is 7.34 indicates that the respiratory acidosis is partially compensated. The bicarbonate concentration is estimated to be 31 mmol/litre (a 7 mmol/litre increase accounting for the compensatory 0.14 increase in pH). This simplified approach works well in everyday clinical practice. When a more meticulous method is desired, an acid–base diagram can be used (Figure 4).

**Diagnosis**

The clinical diagnosis of respiratory failure can be obvious in patients with acute respiratory distress, or more difficult in certain causes of chronic hypoxaemia or hypoventilation.

**Hypoxaemia** leads to central cyanosis, in which circulating deoxygenated haemoglobin is more than 5 g/dl (haemoglobin saturation < about 75% at normal haemoglobin concentrations). Note that cyanosis can occur in polycythaemia, though haemoglobin saturation is increased and arterial oxygen content is relatively normal. Cyanosis is also seen when methaemoglobin is present at more than 1.5 g/dl. Central cyanosis is best seen in the lips and tongue. Peripheral cyanosis usually occurs in conjunction with true central cyanosis, but can occur independently as a result of impaired peripheral circulation and is therefore unreliable as a sign of hypoxaemia in everyday clinical practice.

**Hypercapnia** causes peripheral venous dilatation, tachycardia, increased cardiac output and a large-volume pulse. Severe hypercapnia causes headache from cerebral vasodilatation (often in the early morning on waking), and even papilloedema. Hypercapnia has direct effects on CNS function (asterixis, hyporeflexia, meiosis, confusion and coma – carbon dioxide narcosis).

**Specific physical signs** may be present depending on the cause of respiratory failure. Chest wall deformities are often overlooked on examination. Auscultation can be uninformative, even in the presence of chronic lung disease. Specific neurological signs should be sought if neuromuscular disease is suspected.

**Practice points**

- Assess respiratory failure in terms of failure of oxygenation and failure of ventilation.
- The most common clinical causes are obstructive sleep apnoea, chronic obstructive pulmonary disease, pneumonia and neuromuscular disease.
- Interpret arterial blood gases in three steps – acidosis or alkalosis, primary respiratory change or not, and any compensatory change.
- Indications for intubation are airway protection, refractory hypoxaemia and uncompensated respiratory acidosis.