# Pathophysiology of Respiratory Failure and Indications for Respiratory Support

Kevin E J Gunning

Respiratory failure occurs when there is inadequate exchange of $O_2$ and $CO_2$ to meet the needs of metabolism, which leads to hypoxaemia, with or without hypercarbia. Diagnosis requires measurement of arterial blood gases. That is, the partial pressure of $O_2$ in arterial blood ($P_aO_2$) and the partial pressure of $CO_2$ in arterial blood ($P_aCO_2$). Respiratory failure can be defined as $P_aO_2$ <8 kPa (60 mmHg), or $P_aCO_2$ >6.7 kPa (50 mmHg) in a patient at rest, breathing air at sea level.

Respiratory failure can be divided into:
- type I respiratory failure, in which processes that impair oxygen transfer in the lung cause hypoxaemia (acute or hypoxaemic respiratory failure)
- type II respiratory failure, in which inadequate ventilation leads to retention of $CO_2$, with hypercarbia and hypoxaemia (chronic, ventilatory or hypercapnic respiratory failure).
- 'mixed' respiratory failure, in which there is a combination of type I and type II respiratory failure (acute-on-chronic respiratory failure).

## Pathophysiology

### Type I respiratory failure (Figure 1)

This is the most common form of respiratory failure. The causes of hypoxia can be discussed in relation to the oxygen cascade (Figure 2).

***Low inspired oxygen fraction*** – the alveolar $O_2$ concentration ($P_AO_2$) will fall if the inspired $O_2$ concentration ($F_IO_2$) falls, as determined by the alveolar gas equation (Figure 3). This can be caused by inadvertent hypoxic gas administration, disconnection of the breathing circuit during mechanical ventilation, or an increase in dead space and rebreathing of exhaled gases.

***Low barometric pressure*** – if the barometric pressure ($P_b$) falls (e.g. at high altitude), the inspired $O_2$ partial pressure ($P_IO_2$) falls and $P_AO_2$ will fall, as determined by the alveolar gas equation (Figure 3). At 3000 m, $P_IO_2$ is 13.3 kPa (100 mmHg) and the $P_aO_2$ is 6.7 kPa (50 mmHg).

***Alveolar hypoventilation*** – hypoventilation must be severe to cause hypoxia in a patient with normal lungs. As the alveolar gas equation shows, however, for each unit rise in $P_aCO_2$, the $P_AO_2$ will fall by a constant amount (Figure 3). The equation also shows that hypoxia resulting from hypoventilation can be corrected by increasing the $F_IO_2$.

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### Causes of type I respiratory failure

- Acute asthma
- Acute respiratory distress syndrome (ARDS)
- Pneumonia
- Pulmonary embolus
- Pulmonary fibrosis
- Pulmonary oedema
- Chronic obstructive pulmonary disease (COPD)
- Emphysema

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***Diffusion impairment*** – efficient gas exchange depends on the interface between alveoli and the bloodstream. Disease affecting this interface results in impaired diffusion. The greater the solubility of a gas, the less it is affected by diffusion deficits. $CO_2$ is 20 times more soluble in water than $O_2$ and therefore a diffusion deficit that causes hypoxaemia will not necessarily cause hypercapnia. Diseases causing a diffusion deficit include pulmonary oedema, pulmonary fibrosis and acute respiratory distress syndrome (ARDS, see Gunning, page 66).

### The oxygen cascade
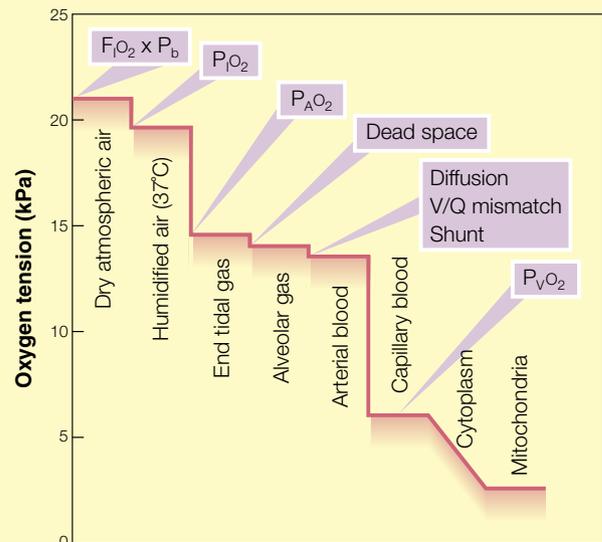


$F_IO_2$ is the fraction of inspired oxygen (0.21 in air)

$P_b$ is the barometric pressure (101 kPa at sea level)

$P_IO_2$ is the partial pressure of oxygen in inspired air
[$P_IO_2 = F_IO_2 \times (P_b - P_{water\ vapour})$]

$P_{water\ vapour}$ is the vapour pressure of water
(6.3 kPa when fully saturated, e.g. in the lungs)

$P_AO_2$ is the alveolar partial pressure of oxygen
[$P_AO_2 = P_IO_2 - (P_aCO_2 / RQ)$]

$P_aCO_2$ is the partial pressure of carbon dioxide in arterial blood

RQ is the respiratory quotient. The ratio of carbon dioxide to oxygen consumption

$P_VO_2$ is the partial pressure of oxygen in mixed venous blood

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## The alveolar gas equation

$P_AO_2 = P_IO_2 - (P_ACO_2/RQ)$

$P_AO_2 = F_IO_2 (P_b - P_{water\ vapour}) - (P_aCO_2/RQ)$

$P_AO_2$ is the alveolar partial pressure of oxygen
$P_IO_2$ is the partial pressure of oxygen in inspired air
$P_ACO_2$ is the alveolar partial pressure of carbon dioxide
$F_IO_2$ is the fraction of inspired oxygen (0.21 in air)
$P_b$ is the barometric pressure (101 kPa, 764 mmHg at sea level)
$P_{water\ vapour}$ is the vapour pressure of water (6.3 kPa when fully saturated, e.g. in the lungs)
$P_aCO_2$ is the partial pressure of carbon dioxide in arterial blood
RQ is the respiratory quotient. The ratio of carbon dioxide production to oxygen consumption (0.7 with fatty acid metabolism and 1.0 for carbohydrates). In a healthy person this is often taken to be 0.8, but in reality it changes with metabolism and dietary intake

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Diffusion impairment plays a minor role in the development of hypoxaemia. Patients with impaired diffusion will become hypoxic during exercise, however, or if they breathe a gas mixture with a low inspired $O_2$ concentration.

***Ventilation/perfusion mismatch*** – a one-to-one relationship of ventilation to perfusion of the lungs results in optimal $O_2$ exchange between alveoli and blood. Hypoxaemia can result when there is inequality in alveolar ventilation and pulmonary perfusion (V/Q mismatch). V/Q mismatch is the most common cause of hypoxia in critically ill patients, and may be caused by:
- atelectasis
- pulmonary embolus
- endobronchial intubation
- patient position
- bronchospasm
- obstruction of the airways
- pneumonia
- ARDS.

Hypoxaemia associated with V/Q mismatch caused by deficits in ventilation can be improved by increasing the $F_IO_2$. If atelectasis is present, positive end expiratory pressure (PEEP) will increase the $P_aO_2$.

***Right-to-left shunt*** occurs when pulmonary venous blood bypasses ventilated alveoli and is not oxygenated. This shunted blood retains the saturation of mixed venous $O_2$ (70–80% in healthy individuals). It then mixes with and reduces the $O_2$ content of the non-shunted blood, causing a fall in $P_aO_2$. In healthy people, a shunt of about 2% of the cardiac output occurs because of drainage of venous blood to the left (arterial) circulation from the Thebesian and bronchial veins. This physiological shunt is well tolerated in people with a normal cardiac output.

Significant shunting causing hypoxaemia can occur with sepsis, liver failure, pulmonary embolism and intracardiac right-to-left shunts. Conditions that cause V/Q mismatch (see above) will cause a shunt if they are severe. If alveoli collapse completely, become consolidated or fill with oedema fluid, V/Q = 0.

Shunted blood is never exposed to alveolar gases, therefore the resultant hypoxaemia cannot be corrected completely by increasing the $F_IO_2$, though alveolar collapse can be reduced by PEEP.

### Type II respiratory failure

Patients with type II failure are unable to eliminate $CO_2$ and the $P_aCO_2$ will rise in inverse proportion to the ventilation (Figure 4), provided the total body $CO_2$ production does not change. Inadequate ventilation may be caused by reduced respiratory drive, an increase in dead space or an increase in $CO_2$ production (Figure 5). It can be corrected by increasing the ventilation using mechanical or pharmacological means (i.e. respiratory stimulants). If patients with type II respiratory failure (Figure 6) are given supplemental $O_2$, they may not initially become hypoxaemic.

***Abnormalities of central respiratory drive*** – reduced central respiratory drive will decrease minute ventilation. This is often the result of the effects of sedative drugs and may be worsened by synergistic drug interactions, altered drug metabolism (hepatic/renal failure), intentional or iatrogenic drug overdose. Other causes include head injury, raised intracranial pressure and central nervous system infection. Severe hypercapnia or hypoxaemia can also depress the respiratory centre, leading to a downward spiral of clinical deterioration. The factors that depress the respiratory centre also tend to depress cerebral function as

## Causes of type II respiratory failure

**Pulmonary**
- Acute severe asthma
- Upper airways obstruction
- Chronic obstructive pulmonary disease (COPD)
- Bronchiectasis
- Obstructive sleep apnoea

**Thoracic wall**
- Chest wall trauma (flail chest)
- Ruptured diaphragm
- Kyphoscoliosis
- Abdominal distension (ascites, blood, surgical packs)
- Morbid obesity

**Central nervous system**
- Coma
- Raised intracranial pressure
- Head injury
- Opioid and sedative drugs

**Neuromuscular**
- Cervical cord lesions (trauma, tumour)
- Spinal cord (poliomyelitis)
- Peripheral nerves (Guillain–Barré syndrome, diphtheria, critical illness polyneuropathy)
- Neuromuscular junction (myasthenia gravis, organophosphorus poisoning, muscle relaxants, botulism)
- Muscular dystrophy

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a whole, leading to a decrease in conscious level, an inability to protect the airways and the risk of respiratory obstruction and pulmonary aspiration.

*Abnormalities of the spinal cord* – injury to the spinal cord will affect the innervation of the diaphragm and thoracic intercostal muscles and cause hypoventilation and retention of secretions. Severe ventilatory failure will occur with cord lesions above the origin of the phrenic nerve (C3, 4, 5), because diaphragmatic function is lost and ventilation is dependent on the accessory muscles of respiration. These patients will require long-term mechanical ventilation, though some cord function can return and the accessory muscles develop with time. The spasticity and muscle atrophy caused by motor neurone disease usually lead to death from respiratory failure and aspiration within 5 years. Poliomyelitis damages the anterior (motor) horn cells in the spinal cord, cranial nerves and even the respiratory centre.

*Abnormalities of the motor nerves* – the ascending polyneuropathy of the Guillain–Barré syndrome can lead to respiratory muscle weakness with a reduced vital capacity and an increased respiratory rate. Patients may develop bulbar dysfunction, with the risk of aspiration. Hypoventilation and respiratory acidosis occur suddenly and patients may have a respiratory arrest because the severity of their condition has not been appreciated.

*Abnormalities of the muscles* – muscular weakness caused by congenital myopathies (e.g. the muscular dystrophies) can ultimately lead to ventilatory failure. Myasthenia gravis, a disorder of the neuromuscular junction, causes a generalized weakness, and ventilation failure can occur in myasthenic crises. Acute exacerbations are often related to infection, and cholinergic crises may result from a relative overdose of anticholinergic treatment. Other conditions that result in impaired transmission

**Pathophysiology of respiratory failure**

**Failure of oxygenation (hypoxaemia, type I failure)**
- Low inspired oxygen partial pressure
- Alveolar hypoventilation
- Diffusion impairment
- Ventilation/perfusion (V/Q) mismatch
- Right-to-left shunt

**Failure of ventilation (hypercapnia, type II failure)**
- Abnormalities of central respiratory drive
- Neuromuscular dysfunction
- Abnormalities of the chest wall
- Abnormalities of the airways
- Abnormalities of the lungs

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at the neuromuscular junction may also cause respiratory failure. Botulinum toxin binds irreversibly to the presynaptic terminals at the neuromuscular junction and prevents acetylcholine release. Organophosphates (insecticides and chemical warfare agents (e.g. sarin)) inhibit acetylcholinesterase and allow a build-up of acetylcholine at the neuromuscular junction. Failure to reverse neuromuscular blockade adequately at the end of surgery will also result in inadequate ventilation.

*Abnormalities of the chest wall (e.g. kyphoscoliosis)* impair the mechanics of ventilation, predisposing the patient to the risk of respiratory failure. Patients with fractured ribs will hypoventilate if they are not given adequate analgesia. This, together with a reduced ability to cough because of pain, will lead to sputum retention and predispose to pneumonia. This is exacerbated if the chest wall is unstable because of a flail segment or an underlying pulmonary contusion. Pneumothorax, haemothorax and pleural effusions of sufficient size can contribute to failure of ventilation and oxygenation.

*Abnormalities of the airways and lungs* – parenchymal diseases of the lung and chronic obstructive airways disease (COPD) cause type I respiratory failure. This may progress to type II respiratory failure as the patient becomes exhausted, leading to mixed respiratory failure. Increases in dead space will reduce effective minute alveolar ventilation. Diseases associated with an increased dead space (e.g. emphysema, pulmonary embolus) can cause hypercapnia, but usually there is a compensatory increase in minute ventilation.

*Increased $CO_2$ production* – fever, an increase in the work of breathing (e.g. because of poor lung compliance or high airways resistance), or excessive carbohydrate intake will increase the $P_aCO_2$ for a given minute ventilation and can exacerbate hypercapnic respiratory failure.

## Diagnosis

A history, physical examination and investigations are required to identify the underlying disease process causing the acute respiratory failure. A full review of the presentation of all the underlying causes is beyond the scope of this article.

Careful clinical examination and blood gas analysis will assist in diagnosis of the underlying condition by identifying the type of respiratory failure.

*Type I respiratory failure* – patients with type I respiratory failure usually have impaired gas exchange with a low $P_aO_2$, a low functional residual capacity (FRC) and reduced pulmonary compliance. Minute ventilation increases in response to lung juxta-capillary receptor stimulation, metabolic acidosis and severe hypoxaemia, reducing the $P_aCO_2$. There is a mechanical advantage to breathing rapidly, with small tidal volumes when the lungs have are stiff and the FRC is reduced.

Patients with type I respiratory failure are therefore hypoxic, hypocarbic and tachypnoeic, and take small breaths.

*Type II respiratory failure* – patients with pure ventilatory failure are hypercarbic and hypoxic, with a low respiratory rate although patients with neuromuscular disease or chest wall injury may be tachypnoeic with small tidal volumes. They may experience extreme dyspnoea before their blood gases deteriorate.

*Mixed respiratory failure* – the two types of respiratory failure may occur together to produce a mixed picture.

Pulmonary parenchymal disease will initially cause acute hypoxaemic respiratory failure, because of V/Q mismatch and shunt. As a result of the increased work of breathing (due to reduced pulmonary compliance), the respiratory muscles then become fatigued and ventilatory failure develops. Arterial $P_aCO_2$ rises, giving a picture of mixed respiratory failure.

Ventilatory failure may also be complicated by the development of pulmonary parenchymal disease. These patients often have a poor cough, are unable to take a deep breath and are at risk from retained secretions, alveolar collapse and nosocomial infection. A reduced level of consciousness, with exhaustion and hypercapnia, also increases the risk of aspiration pneumonitis.

### Indications for respiratory support

Delayed and inadequate treatment of hypoxia leads to cerebral damage and organ dysfunction. Patients still die unnecessarily from hypoxia. Type II respiratory failure is less common than hypoxic respiratory failure and more patients are harmed by the administration of too little $O_2$ than too much. In acute respiratory failure, a $P_aO_2$ <8 kPa (60 mmHg) or an $S_aO_2$ <90%, is an indication for oxygen therapy. There are a wide variety of devices to deliver $O_2$ (Figure 7). The aim should be to maintain an $S_aO_2$ of >92%. The patient should be monitored with pulse oximetry and blood gas analysis performed within 20 minutes. If the $S_aO_2$ is <90% or the $P_aO_2$ is <7 kPa (53 mmHg) in a patient with previously healthy lungs, the $O_2$ concentration should be increased and further blood gases checked. Meanwhile, the underlying condition should be treated.

In the small proportion of patients with chronic obstructive airways disease (COPD) and chronic type II respiratory failure who have lost their hypercapnic drive and rely on hypoxic drive to stimulate ventilation, the inspired $O_2$ concentration should be limited to 24–28% using Venturi-type fixed performance oxygen masks whenever possible. The aim of treatment should be to maintain the $P_aO_2$ at 8–10 kPa (60–75 mmHg).

The expected $P_aO_2$ in room air falls with age, because of an increase in the alveolar–arterial oxygen gradient. There is a great deal of individual variation for the expected $P_aO_2$; average values are shown in Figure 8.

Clinical assessment of patients with respiratory failure is as important as blood gas analysis in assessing the need for ventilatory support. If the hypoxaemia does not improve with oxygen therapy, or the patient becomes exhausted with a rising $P_aCO_2$,

### Arterial oxygen tension and age

| Age (years) | $P_{A–a}O_2$ (kPa)[1] | Expected $P_aO_2$ (kPa) |
|---|---|---|
| 20 | 0.9 | 13 |
| 40 | 1.4 | 12.5 |
| 60 | 2.0 | 11.9 |
| 80 | 2.5 | 11.4 |

[1]$P_{A–a}O_2$ is the alveolar–arterial oxygen gradient

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then transfer to an ICU and mechanical ventilation should be considered.

### Indications for tracheal intubation (Figure 9)

*Protection from aspiration* – patients with bulbar dysfunction (e.g. Guillain–Barré syndrome) or a decreased level of consciousness are at potential risk of aspiration of gastric contents and may require intubation to protect their airways and lungs. A cuffed endotracheal tube is not an absolute guarantee against aspiration, which can still occur around an inflated cuff. Aspiration of gastric contents may predispose to the development of hospital-acquired pneumonia in patients receiving mechanical ventilation. There is some evidence that this can be reduced by nursing all mechanically ventilated patients in a 30° head-up position.

*Facilitation of tracheobronchial suction* – if a patient's cough is ineffective because of pain or weakness, secretions will be retained, particularly when tracheobronchial secretions are excessive. This causes atelectasis, and a worsening of the respiratory failure. Intubation allows tracheal suction to be performed and secretions can be cleared from the large airways.

*Upper airways obstruction* may result from a decreased level of consciousness, oedema, trauma, or a foreign body. Tracheal intubation is required to maintain the airways until the condition has resolved. High-risk patients (e.g. with burns of the airways, laryngeal oedema secondary to anaphylaxis or facial trauma) should be intubated early, because laryngoscopy and intubation may become more difficult over time.

### Indication (Figure 10)

*Support in respiratory failure* – the most common indication for mechanical ventilation outside the operating theatre is as a supportive therapy in the management of respiratory failure.

If the patient is unable to maintain adequate oxygenation

### Oxygen delivery devices

**Variable performance:** the $F_iO_2$ varies with respiratory rate and minute volume

| | |
|---|---|
| Nasal prongs | $F_iO_2$ 25–50% with flows of 1–6 l/minute |
| Hudson mask | $F_iO_2$ 30–50% with flows of 6–8 l/minute |
| Non-rebreathing mask | $F_iO_2$ 60–90% with flow of 15 l/minute |

**Fixed performance**

Ventimask using the Venturi principle: oxygen is delivered to the mask at a given flow rate and a fixed amount of air is entrained so that the $F_iO_2$ can be accurately predicted. Masks delivering 24%, 28%, 34%, 40% and 60% are available.

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### Indications for tracheal intubation

- Facilitation of mechanical ventilation
- Protection from aspiration
- Facilitation of tracheobronchial suction
- Relief of upper airways obstruction

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despite the use of supplemental $O_2$, or their $CO_2$ rises progressively, they may need mechanical ventilation. The decision to start mechanical ventilation should be based on clinical examination and supported by blood gas analysis. Mechanical ventilation should be considered if the $P_aCO_2$ is >7 kPa (53 mmHg) in a patient who usually has a normal $P_aCO_2$, or if the $P_aCO_2$ increases by more than 2 kPa (15 mmHg), especially if accompanied by an acidosis.

Patients who may require mechanical ventilation should be referred to an intensive care physician at an early stage to avoid the need for intubation of the patient *in extremis*. They should be transferred to a critical care or high-dependency area, where they can be observed closely and intubation can be performed if necessary. Clinical features suggesting the need for invasive respiratory support are difficulty in talking, sweating, pursed lips and active use of accessory muscles of respiration. Cardiovascular signs, such as cooling of the extremities, tachycardia, dysrhythmias and a falling urinary output, reflect the increased work of breathing. These signs of acute respiratory distress are sometimes better indicators of the need for ventilation than blood gas results. A high respiratory rate, >30/minute, low tidal volumes, <3–4 ml/kg, and vital capacity <15 ml/kg, often accompanied by disorientation or a deterioration in the level of consciousness, suggest impending exhaustion (Figure 11).

***Control of intracranial pressure*** – a rise in $CO_2$ should be avoided in patients with raised intracranial pressure. $P_aCO_2$ should be maintained at the lower end of the normal range (4.5–5.0 kPa, 33–38 mmHg) in patients with head injuries to reduce cerebral blood flow and to reduce intracranial pressure. An excessive reduction of $P_aCO_2$ should be avoided, because this may cause cerebral vasospasm and cerebral ischaemia.

***Reduction of metabolic demands*** – the cardiovascular system of patients in shock can benefit from the removal of the metabolic demands of diaphragmatic and accessory respiratory muscle contraction.

***Postoperative ventilation*** should be considered in patients at risk of postoperative respiratory failure. This includes patients with severe cardiorespiratory disease, neuromuscular disease or abnormalities of central respiratory drive. Smoking and morbid obesity (body mass index >35) will increase the risk. Thoracic or upper abdominal surgery and emergency surgery carry the greatest risk of postoperative respiratory failure. A period of ventilation after the operation allows the effects of anaesthetic drugs to wear off and the patient to warm up. Patients can then be weaned from the ventilator when they are stable and their pain has been controlled. The risks and benefits of surgery and the

possible need for postoperative ventilation should be considered and discussed with the patient before the operation.

Traditionally, anaesthetic techniques using high doses of opioids have been used in high-risk surgical patients. It is then necessary to ventilate the patient for a period of time postoperatively to allow the effects of these drugs to subside. However, modern anaesthetic and surgical techniques using epidural analgesia and short-acting powerful opioids (e.g. remifentanil) have enabled many patients to recover without the need for postoperative ventilation.

## Prognosis

It is important to make a assessment of the reversibility of a patient's illness and prognosis before starting ventilation. If it is anticipated that a patient's condition might deteriorate to such an extent that ventilation is likely, a discussion should take place before emergency intervention is necessary. This is especially important in patients with chronic illnesses (e.g. COPD). However, the prognosis of many diseases will change with advances in medical therapy. For example, some patients with respiratory failure caused by *Pneumocystis carinii* pneumonitis who had a poor prognosis in the 1980s, may now benefit from respiratory support while the underlying condition is treated. ◆

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### Respiratory parameters in health and in respiratory failure

| | Normal | Respiratory failure |
|---|---|---|
| $P_aO_2$ (kPa) | 10.5–14 | <7 |
| $P_aCO_2$ (kPa) | 4.7–6.0 | >7 |
| Respiratory rate (per minute) | 10–25 | >30 |
| Tidal volume (ml/kg) | 5–8 | <3–4 |
| Vital capacity (ml/kg) | 30–70 | <15 |

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### Indications for mechanical ventilation

- To facilitate major surgery
- Support in respiratory failure
- Coma (head injury, drug overdose)
- Control of intracranial pressure
- Reduction of metabolic demands
- Postoperative ventilation
- Inter- or intra-hospital transfer of the critically ill patient

**FURTHER READING**

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