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Pathophysiology and Classification of Respiratory Failure

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Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchange functions. It is a major cause of morbidity and mortality in patients admitted to intensive care units. It is a result of either lung failure, resulting in hypoxemia, or pump failure, resulting in alveolar hypoventilation and hypercapnia. This article covers the basic lung anatomy, pathophysiology, and classification of respiratory failure. **Key words:** *hypercarbic*, *hypoxemic*, *respiratory failure*, *ventilation/perfusion mismatch*

IN THE UNITED STATES, the incidence of respiratory failure is about 360 000 cases per year and 36% die during the initial hospitalization. It is the third leading cause of mortality in the United States.[1] These rates increase with age and presence of comorbidities. With the current burden of respiratory failure and high associated health care costs, it is prudent that health care providers become aware of the basic pathophysiology and classification of respiratory failure to provide timely and appropriate management.

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ANATOMY OF THE RESPIRATORY SYSTEM

The respiratory system is situated in the thorax and is responsible for gaseous exchange between the circulatory system and the environment. Air is inspired via the upper airways (the nasal cavity, pharynx, larynx, and trachea) into the lower airways (bronchial tree) (Figure 1).

Each branch of the bronchial tree eventually subdivides to form very narrow terminal bronchioles, which end in the alveoli. There are millions of alveoli in each lung. These are the structures responsible for gaseous exchange, presenting a massive surface area for gas exchange to occur.[2] The lungs are divided into lobes. The left lung is composed of the upper lobe, the lower lobe, and the lingula. The right lung is composed of the upper, middle, and lower lobes.[3]

Breathing is facilitated by the intercostal muscles and diaphragm. To take in a breath, the external intercostal muscles contract, moving the ribcage up and out. The diaphragm moves down at the same time, creating negative pressure within the thorax, allowing inspired air to rush in through the upper and lower airways into the alveoli.[2]

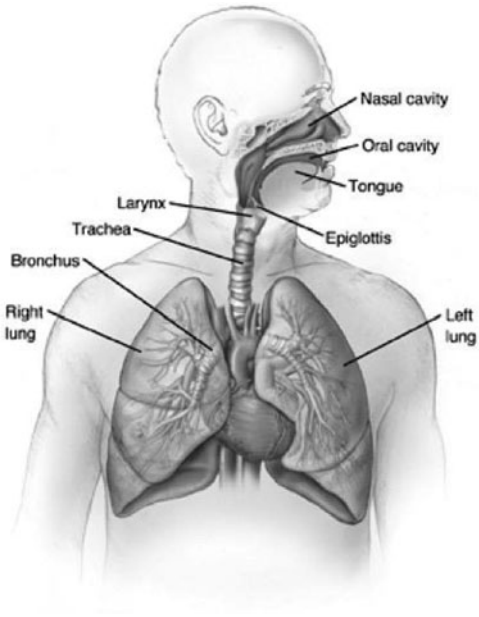


Figure 1. Anatomy of the respiratory system.

Expiration is mainly due to the natural elasticity of the lungs, which tend to collapse if they are not held against the thoracic wall. The lungs are held to the thoracic wall by the pleural membranes, which is a dual layer consisting of parietal and visceral pleura.[4,5]

PHYSIOLOGY OF THE RESPIRATORY SYSTEM

The functioning unit of the lung is alveolus with its capillary network. Various factors govern transport of air from the environment to the alveoli (ventilation) and supply of blood to the pulmonary capillaries (perfusion). Oxygen (O_2) is transported through the upper airways to the alveoli and then diffuses across the alveolocapillary membrane and enters the capillary blood. There, it combines with hemoglobin and is transported by the arterial blood to the tissues. In the tissues the O_2 is utilized for ATP (adenosine triphosphate) production, which is essential for all metabolic processes.[6]

The major byproduct of cellular metabolism, carbon dioxide (CO_2), diffuses from the tissues into the capillary blood, where a major portion of it is hydrated and transported to the lungs by the venous blood. Since the concentration of CO_2 is lower in the alveoli than in blood, CO_2 will move into the alveolus by a simple process called passive diffusion (Figures 2 and 3).[4]

The Henry law dictates that when a solution is exposed to an atmosphere of gas, an equilibration of partial pressures follows between the gas molecules dissolved in the liquid and the gas molecules in the atmosphere.[1] Consequently, at equilibrium, the partial pressure of O_2 and CO_2 results from a dynamic equilibrium between O_2 delivery to the alveolus and O_2 extraction from the alveolus, and CO_2 delivery to the alveolus and CO_2 removal from the alveolus.[7]

Delivery of O_2 to the alveolus is directly related to ventilation rate and partial pressure of O_2 in the inspiratory air, FIO_2. Extraction of O_2 from the alveolus is determined by the hemoglobin level. The O_2 saturation of the hemoglobin in the pulmonary capillary blood is affected by the cardiac output and the extraction of the O_2 by the tissues (metabolism). The partial pressure of O_2 in the alveolus is further affected by the partial pressure of CO_2 in the pulmonary capillary blood.[7,8] Ventilation and perfusion are further influenced by variation in distribution of ventilation and perfusion. The

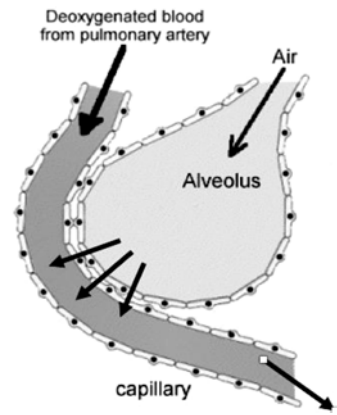


Figure 2. Gas exchange between alveoli and capillaries.

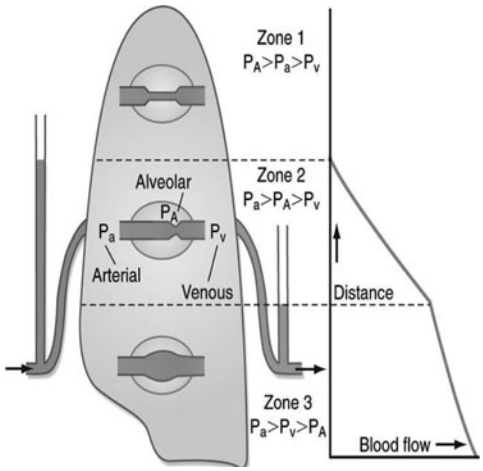


Figure 3. Preferential distribution of ventilation and perfusion in a normal lung.

major determinants of distribution of pulmonary blood flow include cardiac output, pulmonary artery pressure, gravity, posture, and interaction of pulmonary artery pressure with airway pressure and pulmonary venous pressure.[2,9]

In general, perfusion is greater at the lung bases than at the apex and this difference increases with decrease in cardiac output and hypotension and with the application of positive pressure ventilation (Figure 4).

Distribution of ventilation is influenced by regional transpulmonary pressure gradient and changes in the transpulmonary pressure during inspiration. In general, alveolar ventilation is greater in the apical regions than at the base and ventilation is greater at the base than at the apex.[2,9]

EFFECT OF VENTILATION/PERFUSION IMBALANCE

The partial pressures of O_2 and CO_2 in each alveolus and the capillary blood leaving it primarily are determined by the ventilation/perfusion ($\dot{V}A/\dot{Q}$) ratio of that alveolus. As the ratio between ventilation and perfusion decreases, the partial pressure of the O_2 falls and that of CO_2 rises in the blood leaving that alveolus. The opposite occurs as $\dot{V}/\dot{Q}$ ratio increases. Any pathologic process that affects the airways, lung parenchyma, and vasculature of the lungs will cause an imbalance between ventilation and perfusion and will produce areas of abnormal $\dot{V}/\dot{Q}$.[8]

It is important to realize that arterial hypoxemia and hypercapnia result from regions of the lungs with low $\dot{V}/\dot{Q}$ ratio. Areas with high $\dot{V}/\dot{Q}$ ratio do not adversely affect the arterial blood gas tensions; however, they increase the amount of wasted ventilation (this is also called "dead space ventilation"). Theoretically, the most efficient gas exchange would occur if a perfect match exists between ventilation and perfusion in each of the functioning unit of the lung.[10]

The functioning unit (alveoli) can exist in 1 of the 4 absolute relationships [2]:

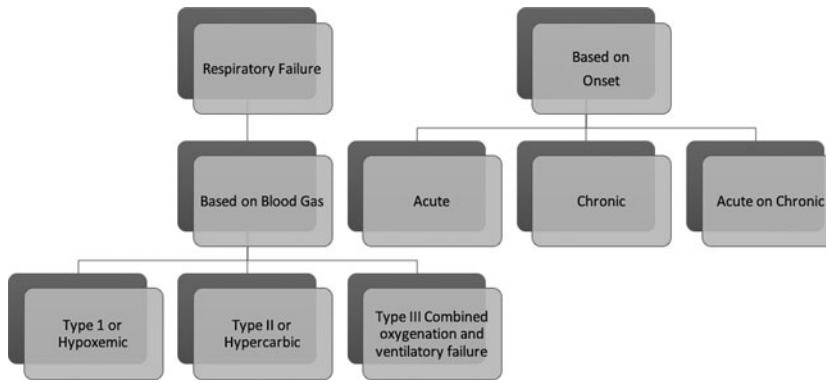


Figure 4. Classification of respiratory failure based on blood gases and onset.

1. The normal unit in which both ventilation and perfusion are matched.
2. The dead space unit in which the alveolus is normally ventilated but there is no blood flow through the capillary.
3. The shunt unit in which the alveolus is not ventilated but there is normal blood flow through the capillary.
4. The silent unit in which the alveolus is unventilated and the capillary has no perfusion.

CLASSIFICATION OF RESPIRATORY FAILURE

As shown in Figure 5, respiratory failure can be classified on the basis of arterial blood gas and onset.[10] The classification is given in this article; however, the management is discussed elsewhere in more details.

Type I or hypoxic respiratory failure

This is the most common form of respiratory failure and is defined as severe arterial hypoxemia that is refractory to supplemental O_2 (PaO_2 <60 mm Hg). Several mechanisms account for the hypoxemia seen in a wide variety of diseases[1,11]:

1. Low inspired oxygen partial pressure
2. Alveolar hypoventilation
3. Diffusion impairment
4. $\dot{V}/\dot{Q}$ mismatch
5. Right-to-left shunt

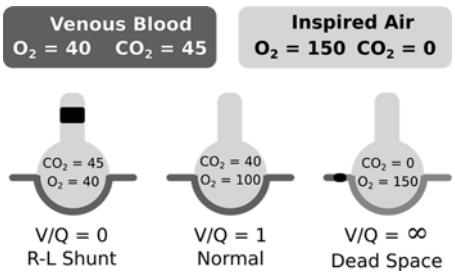


Figure 5. Difference in the physiology of shunt and dead space.

$\dot{V}/\dot{Q}$ *mismatching*

$\dot{V}/\dot{Q}$ mismatching develops when there is decreased ventilation to normally perfused regions or when there are lung regions with a greater reduction in ventilation than in perfusion. One-to-one relationship of ventilation to perfusion of the lungs results in optimal O_2 exchange between alveoli and blood.[1,2] $\dot{V}/\dot{Q}$ mismatch is the most common cause of hypoxia in critically ill patients and may be caused by the following[10,11]:

- Atelectasis
- Pulmonary embolus
- Bronchospasm
- Obstruction of the airways
- Pneumonia
- Adult respiratory distress syndrome (ARDS)
- Patient position

Hypoxemia associated with $\dot{V}/\dot{Q}$ mismatch caused by deficits in ventilation can be improved by increasing the FIO_2. If atelectasis is present, positive end-expiratory pressure will increase the PaO_2.[1,2,11]

Right-to-left shunt

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 nonshunted blood, causing a fall in PaO_2.[2,4,6]

In healthy people, a shunt of about 2% of the cardiac output occurs because of drainage of venous blood to the left (arterial) circulation. This physiological shunt is well tolerated in people with a normal cardiac output. In other words, diseases that decrease the diffusion of oxygen from the alveolar space to the pulmonary capillaries, decrease capillary surface area, or shorten the transit time of the blood through the pulmonary capillaries prevent complete equilibration of alveolar oxygen with pulmonary capillary blood.

Severe hypoxemia can result from disorders in which one or a combination of the aforementioned 3 mechanisms is present. Significant shunting causing hypoxemia can

occur with sepsis, liver failure, pulmonary embolism, and intracardiac or pulmonary anatomic right-to-left shunts. In contrast to $\dot{V}/\dot{Q}$ mismatch or diffusion abnormality, supplemental inspired oxygen does not correct hypoxemia due to right-to-left shunt.[3,5]

Low inspired oxygen fraction

The alveolar O_2 concentration (P_{AO_2}) will fall if the inspired O_2 concentration (F_{IO_2}) falls. 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. There are 2 ways one can have low inspired F_{IO_2}:[2,3,11]

Low barometric pressure: If the barometric pressure (Pb) falls (eg, at high altitude), the inspired O_2 partial pressure (P_{IO_2}) falls and P_{AO_2} will fall.

Alveolar hypoventilation: This also results in type 2 respiratory failure. Hypoventilation must be severe to cause hypoxia in a patient with normal lungs.

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 hypoxemia will not necessarily cause hypercapnia. Diseases causing a diffusion deficit include pulmonary edema, pulmonary fibrosis, and ARDS.[10,11]

Common diseases causing hypoxic respiratory failure

1. ARDS
2. Asthma
3. Pulmonary edema
4. Chronic obstructive pulmonary disease (COPD)
5. Interstitial fibrosis
6. Pneumonia
7. Pneumothorax
8. Pulmonary embolism
9. Pulmonary hypertension

Relationship of ventilation and arterial carbon dioxide tension is as follows:[1,2]

$$P_{aCO_2} = \frac{V_{CO_2}}{V_A}$$

where V_A = alveolar ventilation; P_{aCO_2} = arterial carbon dioxide tension; and V_{CO_2} = carbon dioxide production per minute.

Type II or hypercarbic respiratory failure

The hallmark of ventilatory failure or hypercarbic respiratory failure is the increase in P_{aCO_2}. It is defined as a $P_{CO_2} > 50$ mm Hg (if not a chronic CO_2 retainer). It may occur acutely, insidiously, or acutely superimposed on chronic hypercapnia. In all these conditions, the common denominator is reduced alveolar ventilation for a given CO_2 production. This is usually seen in patients with an increased work of breathing due to airflow obstruction or decreased respiratory system compliance, with decreased respiratory muscle power due to neuromuscular disease, or with central respiratory failure and decreased respiratory drive.[12,13]

Hypercapnia may also result from either increased CO_2 production secondary to increased metabolism (sepsis, fever, burns, overfeeding) or decreased CO_2 excretion.

It is also important to note that CO_2 excretion is inversely proportional to alveolar ventilation (V_A). V_A is decreased if total minute ventilation is decreased secondary to either a decreased respiratory rate (f) or a decrease in tidal volume (V_T) or both or if the dead space fraction of the tidal volume is increased (V_D/V_T).[2]

$$P_{aCO_2} = k \times \frac{V_{CO_2}}{V_A}$$

Therefore,

$$P_{aCO_2} = k \times \frac{V_{CO_2}}{V_E\left(1 - \frac{V_D}{V_T}\right)}$$

$$= k \times \frac{V_{CO_2}}{(V_T \times f)\left(1 - \frac{V_D}{V_T}\right)}$$

Since

$$V_A = (V_T - V_D)f$$

where V_{CO_2} is carbon dioxide production; V_A is alveolar ventilation; V_E is total minute ventilation; and V_D/V_T is the fraction of dead space over tidal volume.[2,13]

As previously noted, hypercapnia signifies the presence of alveolar hypoventilation. This may result from a fall in minute ventilation as explained earlier or an inadequate ventilatory response to areas of low $\dot{V}/\dot{Q}$ imbalance. An abrupt rise in Pa_{CO_2} is always associated with respiratory acidosis.

However, chronic ventilatory failure ($Pa_{CO_2} > 46$ mm Hg) is usually not associated with acidosis because of metabolic compensation. It is the correction of respiratory acidosis (pH < 7.25) that matters, not the correction of Pa_{CO_2}.

Patients with type II failure are unable to eliminate CO_2, and the Pa_{CO_2} will rise in inverse proportion to the ventilation, 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.[14]

Pathophysiology underlying the causes of type II respiratory failure

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), and intentional or iatrogenic drug overdose.

Other causes include head injury, raised intracranial pressure and central nervous system infection. Severe hypercapnia or hypoxemia can also depress the respiratory center, leading to a downward spiral of clinical deterioration. The factors that depress the respiratory center also tend to depress cerebral function as a whole, leading to a decrease in the level of consciousness, 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, C4, C5) because diaphragmatic function is lost. The spasticity and muscle atrophy caused by motor neuron disease usually lead to death from respiratory failure and aspiration. Poliomyelitis damages the anterior (motor) horn cells in the spinal cord, cranial nerves, and even the respiratory center.

Abnormalities of the motor nerves

Ascending polyneuropathy 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.

Abnormalities of the muscles

A weak muscle requires more energy in relation to its maximum energy consumption to perform a given amount of work. The force developed by a skeletal muscle that is sufficient to produce fatigue is a function of the maximum force that the muscle can develop. Any condition that decreases the maximum force decreases the muscle's strength and predisposes to fatigue. Finally, muscle efficiency, the ratio of external work performed to energy consumed, is an important factor in energy demands.[2,15,16]

Inspiratory muscle efficiency is known to fall in patients with hyperinflation. It has been shown that, for the same work of breathing, the oxygen cost is markedly higher in patients with emphysema than in normal subjects. This happens, in emphysematous patients, because either some inspiratory muscles may

contract isometrically (they consume energy but do not perform work) or the inspiratory muscles are operating in an inefficient part of their force/length relationship: a more forceful contraction is required to produce a given pressure change, and an even greater degree of excitation is required to develop a given force. Thus, both conditions lead to increased energy consumption for a given pressure development.

Factors determining the inspiratory muscle energy available are muscle blood flow, arterial oxygen content, blood substrate concentration, and the ability of the muscles to extract energy. Diaphragmatic blood flow is essentially determined by the perfusion pressure, which is a function of cardiac output and peripheral vascular resistance, and the vascular resistance of the muscle, which is a function of the intensity and duration of contraction. Energy supply to inspiratory muscles also depends on the ability of the muscle to increase blood flow in parallel with the increased work.[2,9]

The diaphragm has a greater capacity to increase blood flow than other skeletal muscles. However, the amount that the inspiratory muscle blood flow can be increased may be affected by the intensity and duration of muscle contraction. If the respiratory muscles remain contracted throughout the respiratory cycle, as occurs in asthma, the overall blood flow to the muscles may be less than that required. In addition, hemoglobin concentration and oxyhemoglobin saturation influence the aerobic energy supply to the muscle and hence its endurance.[9]

Conditions characterized by inability of the muscles to extract and use energy, such as sepsis or cyanide poisoning, or diminished energy stores and glycogen depletion, may potentially lead to respiratory muscle fatigue. Therefore, muscle fatigue leads to inability of the respiratory muscles to develop adequate inspiratory pressure during tidal breathing, with consequent decreases in V_T and V_E and hypercapnia.

Muscular weakness caused by congenital myopathies (eg, 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 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 inhibit acetylcholinesterase and allow a buildup 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 (eg, 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 analgesics. This, together with a reduced ability to cough because of pain, will lead to secretion 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, hemothorax, and pleural effusions of sufficient size can contribute to failure of ventilation and oxygenation.[15-17]

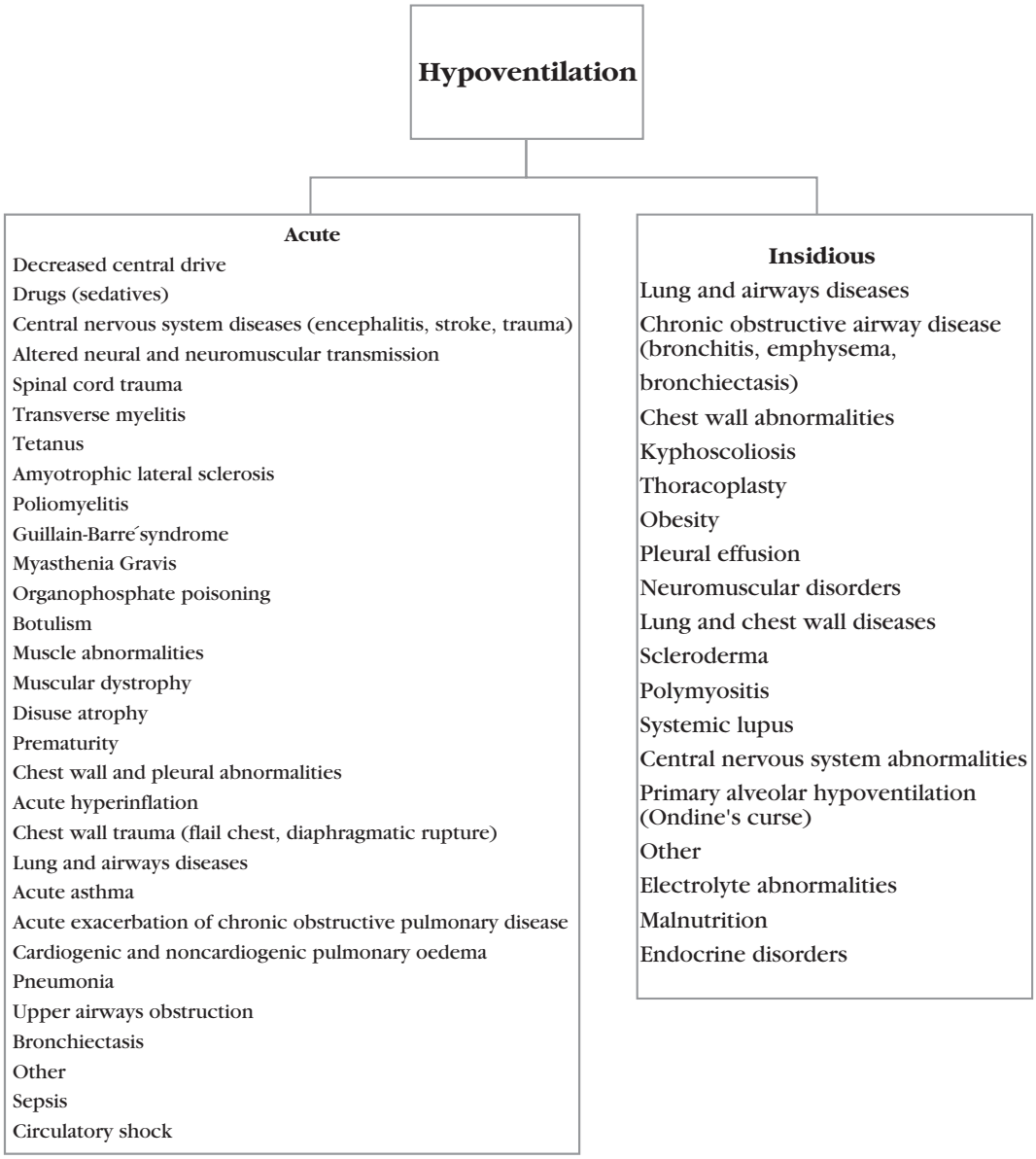
Abnormalities of the airways and lungs

Parenchymal diseases of the lung and 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 (eg, emphysema, pulmonary embolus) can cause hypercapnia, but usually there is a compensatory increase in minute ventilation.[18]

Increased CO_2 production

Fever, an increase in the work of breathing (eg, because of poor lung compliance or high airways resistance), or excessive carbohydrate intake will increase the $PaCO_2$ for a given minute ventilation and can exacerbate hypercapnic respiratory failure.[17-20]

Causes of hypoventilation based on onset



Disease process causing type II respiratory failure

Pulmonary
- Acute severe asthma
- Upper airways obstruction
- COPD
- Bronchiectasis
- Obstructive sleep apnea

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, tumor)
- Spinal cord (poliomyelitis)
- Peripheral nerves (Guillain-Barre′ syndrome, diphtheria, critical illness polyneuropathy)
- Neuromuscular junction (myasthenia gravis, organophosphorus poisoning, muscle relaxants, botulism)
- Muscular dystrophy

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