Acute Respiratory Failure
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Respiratory failure can be defined as the inadequacy of the respiratory system to handle its main responsibilities for gas exchange, intake of oxygen, and elimination of carbon dioxide. Respiratory failure is generally characterized as either hypercapnic, when ventilation is insufficient to maintain a normal PaCO\(_2\) (i.e., <45 mm Hg), or hypoxic, defined as a PaO\(_2\) less than 55 mm Hg. In clinical practice, the term is also used to describe any state in which the patient appears to have difficulty breathing.

Both forms of respiratory failure can be acute or chronic. Signs of chronic hypoxemia include polycythemia, cyanosis, cor pulmonale, or simply a low PaO\(_2\) in someone who appears comfortable and not dyspneic. Chronic hypercapnic respiratory failure has a characteristic appearance in terms of laboratory values. The arterial blood gas shows elevation of PaCO\(_2\), without significant acidosis due to the accompanying metabolic alkalosis, which is seen on the electrolyte panel represented by an elevated bicarbonate level. For patients with chronic respiratory failure, every increase in PaCO\(_2\) by 10 mm Hg will be accompanied by a decrease in pH of 0.03. In a patient with acute respiratory acidosis, for every increase in PaCO\(_2\) of 10 mm Hg, the pH will decline by 0.08. If this ratio of PaCO\(_2\) to pH does not match the values that indicate either acute (10:0.08) or chronic (10:0.03) respiratory failure, then one should consider the possibility of acute-on-chronic hypercapnic respiratory failure.
Often, acute hypoxemia can occur with chronic hypercapnia (i.e., pneumonia in someone with advanced emphysema). Evidence of this can also be found in the laboratory values. For example, when a patient who has chronic hypercapnia becomes acutely hypoxic, he or she will hyperventilate to raise $P_o_2$. This will pseudo-normalize the $P_Co_2$ and accentuate the alkalosis. In patients with hypoxia who are found to have unexplained metabolic alkaloses, chronic lung disease should be considered.

**HYPOXEMIC RESPIRATORY FAILURE**

The principal mechanisms of hypoxemic respiratory failure can be separated into intrapulmonary and extrapulmonary factors. The extrapulmonary abnormalities include low inspired partial pressure of inspired oxygen ($P_{io_2}$) and low oxygen delivery to the tissues resulting in tissue hypoxia. The 4 intrapulmonary factors include hypoventilation, shunt, ventilation/perfusion (V/Q) inequality or mismatch, and diffusion limitation or abnormality. The intrapulmonary causes are more common and will be discussed at length individually.

**Extrapulmonary Causes of Hypoxemia**

**Low Oxygen Environment**

One cause of extrapulmonary hypoxic respiratory failure is low $P_{io_2}$, which is uncommon but can result from high-altitude and technical misadventures. In these cases, alveolar–arterial gradient ($P_{ao_2}-P_{ao_2}$) is normal and thus lung function is normal.

$$P_{ao_2}-P_{ao_2} = F_iO_2(P_{atm} - PH_2O) - P_{ao_2}R - P_{ao_2}$$

where $F_iO_2$ is fraction of inspired oxygen, $P_{atm}$ is atmospheric pressure, $PH_2O$ is water vapor pressure, and $R$ is respiratory exchange ratio ($V_{O_2}/V_{CO_2}$) ($V_{O_2}$ and $V_{CO_2}$ are oxygen consumption and production, respectively).

Decreases in $F_iO_2$ or $P_{atm}$ via travel to altitude will functionally decrease $P_{ao_2}$ and lead to hypoxemia despite normal lung function.

**Low Mixed Venous Oxygen**

Low oxygen delivery states result in tissue hypoxia and generation of lactic acid due to a supply and demand mismatch. Because the tissues are oxygen avid, their extraction increases until demand outstrips supply and they become anaerobic and begin to generate lactate. These shock states share a common end point of low mixed venous oxygen as a representation of poor oxygen delivery. Any state resulting in disruption of oxygen delivery can cause hypoxia. Low mixed venous oxygen as an isolated cause of hypoxia is uncommon and generally only occurs in the presence of other intrapulmonary abnormality, such as shunt, V/Q mismatch, or diffusion abnormality.

$$D_o_2 = \text{Cardiac Output} \times \text{Carrying Capacity}$$

$$= \text{Cardiac Output} \times [(Hgb \times \% \text{ Saturation of } Hgb \times 1.34) + P_{ao_2} \times 0.003]$$

where $D_o_2$ is oxygen delivery, $Hgb$ is hemoglobin (g/dL), 1.34 is the amount of oxygen carried by $Hgb$ (mL/g), and $(P_{ao_2} \times 0.003)$ is the amount of oxygen dissolved in plasma.

**Intrapulmonary Causes of Hypoxemia**

**Shunt**

Shunt is characterized by perfusion without ventilation. Hypoxemia due to shunt is not reversible with increases in $P_{io_2}$. Shunts can be either intracardiac or intrapulmonary in nature. In either case, mixed venous blood from the right side of the heart enters the left atrium without contacting alveolar gas. Intracardiac shunts are direct right-to-left communications that include patent foramen ovale, patent ductus arteriosus, and atrial or ventricular septal defects. Intrapulmonary shunts include abnormal connections between pulmonary arteries and pulmonary veins such as arteriovenous malformations or cirrhosis. Vascular arteriovenous shunts often can be diagnosed with contrast echocardiography, in which air bubbles injected into the venous circulation arrive at the left atrium, indicating that they have not been filtered by the lung's capillary bed. The timing of arrival of the bubbles to the left atrium helps to determine whether the shunts are intracardiac or
intrapulmonary in nature, the former arriving within 1 to 3 cardiac cycles.

Physiological shunting is also commonly found in states of dense alveolar filling or collapse such as atelectasis, pneumothorax, central airway obstruction, or compressive atelectasis due to abdomen or pleural effusions. In these conditions, hypoxic vasoconstriction reduces much of the blood flow through the nonaerated lung zones but not all. Alveolar filling processes caused by pneumonia, ARDS, alveolar hemorrhage, and congestive heart failure have elements of shunt and ventilation perfusion mismatch and could be considered in a discussion of either topic.

Ventilation/Perfusion Mismatch

This is probably the most common cause of hypoxemic respiratory failure. Optimal gas exchange is based on maximal matching of ventilation and perfusion, that is, a V/Q ratio equal to 1. In the normal lung there is heterogeneity of V/Q matching, but the summation of the 300 million alveoli is a normal distribution around V/Q ratio equal to 1. In disease states, regional mismatching of ventilation to perfusion within the lung leads to ineffective gas exchange. This can be either regional vascular dropout leading to a high V/Q process like chronic obstructive pulmonary disease (COPD) and pulmonary embolism or an alveolar filling process leading to a low V/Q state. At the extremes of this spectrum are shunt (V/Q = 0) and dead space (V/Q = infinity) (See figure 1 on page 317). Some of the

Figure 1.

V/Q is Spectrum of Diseases

Spectrum of diseases involving V/Q. ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; PNA, pneumonia, V/Q, ventilation/perfusion ratio.
most common conditions associated with abnormal V/Q matching are described in more detail next.

**Pneumonia**
Pneumonia is inflammation and infection of the lower respiratory tract and alveoli due to either virus or bacteria. Classically, it presents with a clinical history of increasing cough, purulent phlegm, fevers, dyspnea, and focal examination findings. Unfortunately, the sensitivity of a clinical diagnosis ranges from 50% to 80%. Pneumonia represents the ability of a particular virus or bacteria to overcome the natural defense mechanisms of lung, including barrier function, mucociliary clearance, and the innate and the adaptive immune response. The lungs are constantly bombarded with environmental insults (daily alveolar ventilation of 7000-10,000 L/d) and in general do a good job of maintaining health. A breach in these defense mechanisms can be related to the virulence of organism, the size of the inoculum (eg, aspiration event), a particular deficiency of the individual patient (immunoglobulin G deficiency, HIV, CFTR gene mutation), or mucociliary clearance disruption (as in postinfluenza pneumonia). When defense mechanisms are disrupted, the lower airways and alveoli begin to fill with purulent material over time. This material is composed of bacteria and cells, both alive and dead, and exudative fluid resulting from disruption of basement membranes and cellular tight junctions. Eventually the disruption in alveolar ventilation reveals itself as hypoxemia due to low V/Q and in extreme areas of shunt (V/Q = 0).

**Cardiogenic Pulmonary Edema/ Congestive Heart Failure**
Pulmonary edema is characterized by fluid accumulation in the interstitium and alveolus due to disruption of the process that regulates the direction and rate of fluid exchange. Classically, this accumulation of fluid outside the capillary is described as either cardiogenic, due to problems at the level of the left heart leading to changes in capillary hydrostatic changes, or noncardiogenic, due to oncotic pressure changes and/or capillary permeability changes. In cardiogenic pulmonary edema, the final common pathway is an elevated left atrial pressure with ensuing elevations in pulmonary venous hydrostatic pressure within the capillary bed. This elevation in left atrial pressure may reflect valvular disease like mitral stenosis, diastolic relaxation abnormalities due to ischemia, or chronic hypertension or systolic dysfunction.

The causes of hypoxemia are at least 3-fold for patients with congestive heart failure. Early in the course, congestive heart failure is represented by primarily interstitial fluid, and thus diffusion abnormality may be the primary driver of hypoxemia. This interstitial fluid also can promote areas of low V/Q. It does this by at least 2 mechanisms. First, as lung compliance declines because of accumulation of fluid, there are regional declines in ventilation leading to low V/Q. Second, as fluid continues to enter the interstitium, the airways surrounded by this interstitial fluid become narrowed, leading to a further decline in ventilation. Clinically, this narrowing of airways presents as the classic cardiac wheeze. As the disease progresses, alveolar flooding takes place and areas with low V/Q begin to convert to shunt and progressive hypoxemia.

**Noncardiogenic Pulmonary Edema, Acute Lung Injury, and Acute Respiratory Distress Syndrome**
The initial unifying feature of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is increased capillary permeability due to either direct lung infection or systemic inflammation. The common end point is diffuse damage to the alveolar-capillary membrane. This leak of protein and fluid progresses pathologically and is represented by the appearance of the classic hyaline membranes lining the alveoli. It then is followed by what is described as the proliferative phase of injury with fibrin deposition and inflammatory cell infiltration. The final stage of this disease results in fibrosis of the alveolar ducts, alveoli, and interstitium. The clinical criteria for ARDS include acute onset without evidence of pulmonary edema (pulmonary capillary wedge pressure <18), bilateral alveolar infiltrates, and a Pao2 to Fio2 ratio (P:F) of less than 200. The definition of ALI is the same except for a P:F ratio of less than 300.
The hypoxemia associated with ARDs is the result of several elements. In the early phase of increased permeability, there is regional homogeneity of the fluid extravasation and thus hypoxemia is initially driven by low V/Q diffusely. As this progresses, computed tomography scan imaging data suggest that dependent portions of the lung become less ventilated and eventually atelectatic while the more anterior portions of the lung become overdistended. Interventions like recruitment maneuvers and proning may improve this hypoxemia and the P:F ratio but have not consistently been shown to improve mortality rate.

Treatment of ARDS is guided by the 2 principles: (1) reducing alveolar collapse through the use of positive end-expiratory pressure and (2) using small tidal volumes to limit damage to open lung segments and not overdistend them. In 2001, the ARDS Network demonstrated in a randomized, controlled trial of 861 patient with ARDS that mechanical ventilation with low tidal volumes (6 cc/kg of ideal body weight) and plateau pressures less than 30 mm Hg produced a 9% reduction in mortality (from 40% to 31%). Other clinical and animal studies have demonstrated that high pressure and high tidal volumes are associated with inflammation in lung and serum with injury to the lung and other distant organs.

**Diffusion Abnormalities**

Diffusion is the main method of gas movement in the distal small airways and of gas movement and exchange in the alveoli. Gas exchange is dependent on an intact alveolar–capillary membrane, the partial pressure of the gas diffusing between the 2 compartments, and the time that individual red cells spend in the capillary bed to allow for complete gas exchange. The rate of oxygen binding to the hemoglobin molecule is nonlinear and increases with each individual oxygen molecule it binds. This maintains the maximal pressure gradient between the oxygen in the alveoli and the partial pressure of oxygen dissolved in plasma while in the capillary bed and thus allows for extremely efficient transfer of oxygen across the alveolar–capillary membrane. The time that a red blood cell spends in the capillary bed in a normal patient is 2- to 3-fold that which is required to achieve complete uploading of oxygen. Consequently, diffusion is rarely impaired.

Diseases that classically affect diffusion include pulmonary hypertension and interstitial diseases. The alveolar–capillary membrane is so efficient and redundant that patients are generally not hypoxic until very late in the disease process or with exertion. Hypoxemia with exertion can be explained in part by a decreased time for diffusion to occur across the alveolar–capillary membrane attributable to increases in flow through the capillary bed. The normal response to exertion is to increase cardiac output and recruit pulmonary vascular units, thus causing a decline in pulmonary vascular resistance. Patients with pulmonary hypertension or interstitial disease are unable to recruit pulmonary vascular units; thus, flow rates through the capillary bed increase, leading to a decrease in time for uptake of oxygen in the capillary unit.

**Hypoventilation**

This can be considered the final common pathway for all causes of respiratory distress and is discussed in more detail in the following section.

**HYPERCAPNIC RESPIRATORY FAILURE**

If one considers the lungs as a pump that moves oxygen in and carbon dioxide out, hypercapnic respiratory failure can be viewed as pump failure. Under normal conditions, the level of Pco₂ varies directly with minute ventilation (MV), and the hallmark of hypercapnic respiratory failure is an elevated Pco₂ seen on arterial blood gas studies. Sometimes, under abnormal conditions, the relationship between the observed MV and the Pco₂ can become uncoupled and even move in the opposite direction as is seen in states of increased dead space fraction or ineffective breathing. Thus, hypercapnic respiratory failure can be divided into 2 categories: states of low MV and states of high dead space. Although many conditions lead to both forms of respiratory failure, this section is limited to only acute conditions.
Hypercapnic Respiratory Failure From States of Low Ventilation

Secondary Hypoventilation (Fatigue)
Perhaps the most common reason for an elevated $P_{CO_2}$ in a patient with respiratory failure is fatigue brought on by excessive demand. Anything that causes acute hypoxia or acute acidosis will increase $MV$ in a normal person. The demands can exceed the person's ability to sustain this level of ventilation and respiratory muscle fatigue will begin. Fatigue can occur quickly or slowly over time. Testing blood gases to assess for metabolic acidosis or calculating an alveolar–arterial gradient can be helpful to distinguish patients who have primary hypoventilation (low $P_{O_2}$, high $P_{CO_2}$, normal alveolar–arterial gradient) from those who have fatigue from compensating for primary hypoxia (low $P_{O_2}$, high $P_{CO_2}$, elevated alveolar–arterial gradient) or a metabolic acidosis.

Another important factor is a patient's respiratory muscle strength. Those who are strong and healthy may be able to sustain long periods of hypoxia or acidosis without fatigue. Those who are not or who have underlying chronic conditions that limit ventilation, such as COPD, chest wall abnormalities, or neuromuscular diseases, may tire rapidly and with minimal new demands. Many episodes of respiratory failure are of mixed cause, with fatigue usually being the second component. It is important to look past the hypoventilation at what may have precipitated it.

Primary Hypoventilation
There are so many causes of primary hypoventilation that they are best considered in broad categories and not as individual diseases or conditions. Most conditions that cause hypoventilation generally cause chronic respiratory failure and thus a clue to their presence often lies in evidence of chronic hypoventilation such as elevated bicarbonate or a compensated respiratory acidosis. A useful way to approach a patient with an unexplained primary hypoventilation is to consider, from start to finish, the pathways and mechanisms by which we breathe.

Central Nervous System Disorders
The central nervous system (CNS) initiates and regulates both the rate of breathing and the drive to breathe. Thus, anything that can affect the CNS can influence ventilation. Perhaps the most common culprits in acute respiratory failure are sedating drugs such as opiates, ethanol, or benzodiazepines. Additionally, injury to the brain and brainstem can depress respiration, with traumatic brain injury, cerebral edema, anoxic brain injury, intracranial hemorrhage, and stroke being the most common. When these disorders affect breathing, there is almost always a decrease in the level of consciousness.

Motor Neuron Problems
The spinal cord is a common site of injury that can lead to hypoventilation. Injury to the upper cervical cord (above C3) can eliminate all ventilation through paralysis of the diaphragm and the intercostal muscles. Injuries to C3-C5 will have variable effects on respiration depending on the amount of injury to the spinal cord at the level. Injuries below C3-C5 will paralyze only the intercostals but allow diaphragmatic breathing. Injury is usually in the form of trauma but can also occur through infections, stroke, or tumor. Diseases such as amyotrophic lateral sclerosis and transverse myelitis can paralyze or weaken the muscles of respiration at the level of the spinal cord.

Peripheral nerve dysfunction can cause acute respiratory failure but is less common. Following trauma or thoracic surgery, phrenic nerve injury can lead to respiratory failure and can be difficult to diagnose through routine examination and radiological studies. Several types of progressive paralyses can lead to respiratory failure, such as Guillain-Barré syndrome and myasthenia gravis. Patients can acquire a neuromyopathy from critical illness that can be severe enough to compromise respiration, but this more commonly manifests as failure to wean from mechanical ventilation than it does as a primary cause of respiratory failure.

Medications can cause peripheral nerve dysfunction. In the ICU, prolonged neuromuscular blockade following the use of these agents is a well-known complication.
It often results from impaired clearance of the drug or incorrect dosing but can be idiopathic. Toxins too can cause respiratory muscle dysfunction. Although uncommon in developed nations, tetanus, botulism, and organophosphate poisoning are common causes of respiratory failure in the developing world.

Most causes of neuromuscular dysfunction cause chronic hypoventilation. Their role in acute respiratory failure is attributable in part to the fact that these patients have limited respiratory reserve, and thus small insults such as medications or fatigue can have a disproportionately large impact. The most common scenario by which these conditions lead to acute respiratory failure is dysfunction of the muscles of the upper airway, which can precipitate aspiration and pneumonia.

**Respiratory Muscle Dysfunction**

Respiratory muscle dysfunction can occur in 2 ways. On the cellular level, muscle dysfunction most commonly occurs through malnutrition, fatigue, or electrolyte disorders such as hypophosphatemia or hypokalemia. It can also occur through congenital diseases such as muscular dystrophy or mitochondrial myopathies. Primary muscle dysfunction alone rarely causes acute respiratory failure but contributes by limiting a patient's reserve in times of distress. Some mitochondrial myopathies can worsen in times of malnutrition or stress and cause precipitous declines in strength. Respiratory muscle dysfunction on a larger scale is generally grouped with chest wall disorders as a cause of respiratory failure.

The second way that respiratory muscle function can be impaired is through disorders of the chest wall and its mechanics. These are rarely the sole cause of respiratory failure but can be a secondary contributor. Common acute conditions are burns and trauma, and kyphoscoliosis is a well-known chronic condition. Increasingly, clinicians are seeing obesity-related conditions that can either mimic (obstructive sleep apnea) or exacerbate (obesity hypoventilation syndrome) acute respiratory failure.

**Hypercapnic Respiratory Failure From Increased Dead Space**

Respiratory failure from increased dead space is usually related to air trapping from an obstructive lung disease but can sometimes come from pulmonary vascular conditions such as pulmonary embolism. As the dead space fraction increases, it negatively affects breathing in 2 ways. First, it requires more MV (and thus more work) to accomplish the same amount of oxygenation. Second, for a fixed MV, alveolar ventilation decreases as dead space increases.

In obstructive airway disease like COPD, this process can create a downward spiral into respiratory failure. Some initial insults (such as a pneumonia) result in new or worsening hypoxemia. The response is to increase MV by raising the respiratory rate. Higher respiratory rates result in shorter expiratory times and thus more air trapping. As air trapping increases dead space, ventilation becomes less efficient and alveolar ventilation is further reduced. Conversely, the initial insult could be something that increases airway obstruction, such as bronchospasm.

For patients with end-stage lung diseases like COPD or pulmonary fibrosis, any cause of tachypnea can precipitate the downward spiral by increasing the dead space fraction. As one breathes faster, tidal volumes shrink as muscle fatigue sets in. Since there is a fixed amount of anatomical dead space in the lung from the large airways, shallow breathing alone increases the dead space fraction and thus decreases the alveolar ventilation. This ineffective ventilation can precipitate respiratory failure in patients with advanced lung diseases.

Conditions of the pulmonary vasculature can increase dead space as well. In cases of large pulmonary emboli, all lung distal to the clot becomes dead space. This is reflected in the clinical observation that many patients with pulmonary emboli feel severe dyspnea and yet have little hypoxia.
OTHER CAUSES OF RESPIRATORY FAILURE

One important cause of respiratory failure that should not be overlooked is upper airway obstruction. The obstruction can come from a foreign body such as food but can also result from conditions such as upper airway tissue edema (tongue, epiglottis, larynx), blood clots from upper airway bleeding, and acute vocal cord dysfunction. Patients with decreased mental status or poor cough are particularly susceptible to these conditions. Before any other efforts are made to treat or diagnose an episode of acute respiratory failure, the airway needs to be evaluated for patency.

Several conditions can mimic respiratory failure by increasing sensations of dyspnea or inducing tachypnea. In some patients, these conditions can lead to respiratory failure through fatigue. One of the most common is a metabolic acidosis that causes a compensatory increase in the MV. When an initial workup reveals normoxia and no clear pathological condition in a patient with respiratory distress, acidosis should be considered. Psychiatric conditions, such as panic attacks or anxiety, can also mimic respiratory failure. Vocal cord dysfunction syndrome involves paradoxical vocal cord motion associated with psychosocial disorders that can mimic asthma and respiratory distress. In rare cases, it can precipitate true respiratory failure.

GENERAL APPROACH TO THE PATIENT WITH RESPIRATORY DISTRESS

A systematic approach is recommended for the assessment of a patient with respiratory distress with emphasis on the prompt establishment of adequate oxygenation, control of the airway, and ventilatory support if needed. Once these are established, efforts should focus on establishing the cause of the respiratory failure to guide treatment.

It is important to establish 3 simple facts at the outset. Is there a patent airway? Is the patient normoxic or hypoxic? Is the patient hemodynamically stable? A history of the event and a thorough physical examination should be obtained. Often, this alone will provide the diagnosis. An arterial blood gas study can be helpful in identifying primary hypoventilation from fatigue or acidosis and can provide a rough assessment of the patient’s true effective MV. An example of a systematic approach to evaluating a patient with respiratory failure based on a few key pieces of data can be found in Figure 2 on page 323.

SUMMARY

The most important concerns when treating a patient with respiratory failure are to first secure the airway and stabilize the patient and then to consider all possible causes. Being too quick to arrive at a cause may prevent one from identifying the true cause. A large percentage of respiratory failure events involve multiple factors working together such as pneumonia and bronchospasm or depressed CNS and aspiration. Being aware of all pathological processes will greatly enhance the treatment of the event.

BIBLIOGRAPHY


Evaluation of the patient with respiratory distress. PE, pulmonary embolism; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CNS, central nervous system.