Acute Respiratory Failure

3

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Critical Points

1. A working knowledge of the pathophysiology of acute respiratory failure is necessary to tailor therapeutic maneuvers.
2. The respiratory system has two goals: ventilation and oxygenation. Both goals require work, which is due to both resistance and elastance.
3. The most common causes of hypoxemic respiratory failure are ventilation–perfusion mismatch and shunt.
4. Ventilatory failure is caused by any CO_2 load that is unable to be managed, either through decreased efficiency or drive or through increased production.
5. Ventilatory and oxygenation failure have varying invasive and noninvasive mechanical ventilation requirements, which should be optimized early by the emergency physician to improve outcomes and limit ventilator-induced lung injury.

Introduction

The respiratory system is a highly coordinated set of organs designed to accomplish two important goals: provide oxygen for aerobic metabolism and eliminate cellular waste in the form of carbon dioxide (CO_2). The respiratory system comprises the following:

- *Neurologic system*: The respiratory center in the medulla, phrenic nerve, and neuromuscular membrane coordinate muscular activity and adjustments to metabolic demand.
- *Upper airway*: It provides the conduit from the external environment to the lungs that regulates the temperature and humidity of the air entering the respiratory system and provides the first line of immunologic defense.
- *Lower airway*: The increased cross-sectional area at the lower airways allows flow to become diffusion rather than convection, allowing gas exchange to occur.
- *Cardiovascular system*: It fuels the respiratory pump and delivers CO_2 for exhalation, while supplying the respiratory pump with oxygen to perform work.
- *Lungs*: They provide the surface area for gas exchange.
- *Chest wall/diaphragm*: Because ambient air pressure cannot be altered to provide flow of air into the lungs, the chest wall and diaphragm are

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designed to lower intrathoracic pressure allowing air to flow down the pressure gradient from the external environment. This process makes breathing a metabolically active process. Exhalation, normally achieved by passive recoil of the chest wall and diaphragm, becomes an active process in pathologic conditions such as obstructive lung disease. This active exhalation greatly increases the work of breathing.

The two goals of respiration (eliminating CO_2 and providing adequate oxygen) require work. Work of breathing is the combination of resistive and elastic forces that inhibit airflow over a respiratory cycle. Resistive work of breathing is the work required to overcome resistance to airflow. The larynx provides a point of fixed resistance that must be overcome with normal respiration and can greatly increase the work of breathing due to increased resistance in laryngeal or subglottic disorders, such as laryngospasm, vocal cord dysfunction, and croup. Bronchospasm and mucosal inflammation are common etiologies of dramatically increased work of breathing in asthma exacerbations. Elastic work of breathing is that which overcomes the lung's desire to be at residual volume. Fibrotic lung disease and breathing at higher lung volumes such as the case with obstructive lung diseases increases the elastic work of breathing. The total work of breathing is the work per breath (both resistive and elastic) multiplied by the respiratory rate. Acute respiratory failure (ARF) occurs when any process prevents the respiratory system from adequately maintaining acid–base balance with CO_2 elimination or providing an adequate oxygen supply to maintain aerobic metabolism.

Pathophysiology

With any process that either increases work of breathing beyond the respiratory system's compensatory capacity or limits the respiratory system's ability to eliminate CO_2 or supply adequate oxygen, acute respiratory failure (ARF) occurs. There are four types of respiratory failure (Fig. 3.1):

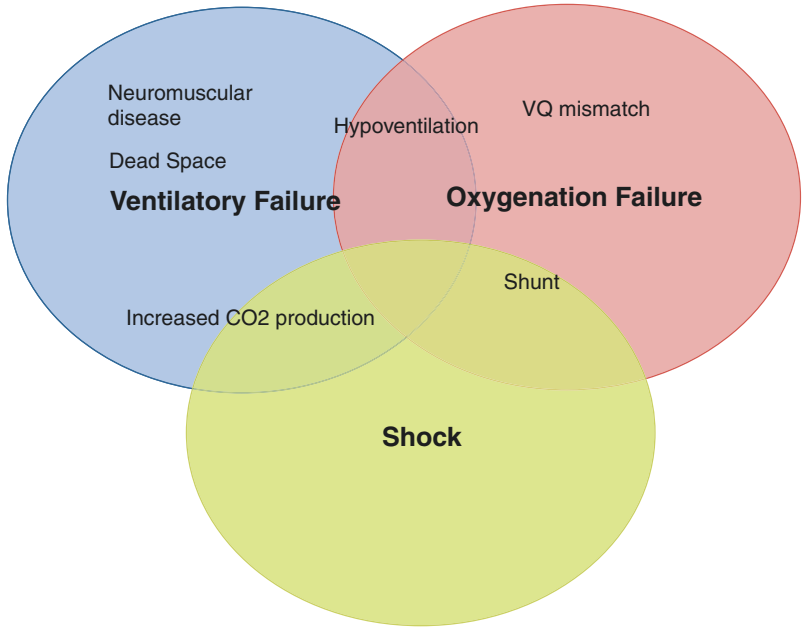

Fig. 3.1 Pathophysiology of acute respiratory failure. Acute respiratory failure can be due to ventilatory failure from hypercapnia (Type II), which is induced by hypoventilation, neuromuscular disease or chest wall abnormalities, increased dead space, or increased work of breathing. Ventilatory failure can also be secondary to increased CO_2 production seen in shock or toxic ingestions. Oxygenation failure (Type I) is most commonly due to VQ mismatch and shunt. Some precipitants of respiratory failure can cause both ventilation and oxygenation defects.

- *Type I* (hypoxemic respiratory failure): Most commonly due to shunt or ventilation/perfusion (*V*/*Q*) mismatch due to airspace disease or anatomic shunt.
- *Type II* (hypercapnic respiratory failure): Most commonly due to a decrease in alveolar ventilation.
- *Type III* (perioperative or mixed respiratory failure): Mixed hypoxemia and hypercapnia, most commonly due to atelectasis.
- *Type IV* (respiratory failure secondary to shock): Most commonly due to increased work of breathing or hypoperfusion to the respiratory muscles, endotoxemia, pulmonary hypertension, and hemorrhage.

Hypoxemic Respiratory Failure

Hypoxemic (Type I) respiratory failure occurs from any etiology that prevents the respiratory system from providing adequate oxygen for delivery to the cells. Hypoventilation can lead to hypoxemia due to the increased partial pressure of CO_2 in the alveolar space displacing oxygen [1]. Similarly, decreased barometric pressure at high elevations leads to a lower oxygen tension in the alveoli at any level of CO_2, given fixed fraction of inspired oxygen, nitrogen, and water vapor [2]. Diffusion abnormalities increase the distance for oxygen diffusion across the alveolar–capillary membrane and can cause hypoxemia in times of increased demand such as high cardiac output states [3]. Additionally, a low mixed venous oxygen saturation can result in systemic hypoxemia in patients with high cardiac output requirements and/or shunt physiology [4]. However, the most common clinically significant precipitants of hypoxemic respiratory failure are *V*/*Q* mismatch and shunt physiology [3].

Any deviation from the optimal ratio of alveolar ventilation to perfusion leads to *V*/*Q* mismatch. A disruption in this ratio leads to alveoli that are either relatively underperfused or underventilated. When alveoli have a relative lack of blood supply for the level of ventilation it receives, those alveoli have a high *V*/*Q* ratio or relative dead space. The respiratory system compensates by increasing blood supply to these areas through hypoxic vasoconstriction of other areas of the lung, optimizing *VQ* mismatch [5]. Disrupting this relationship can lead to hypoxemic respiratory failure. The opposite *V*/*Q* abnormality, perfusion that does not participate in gas exchange, leads to shunt physiology. Due to no ventilation, these alveoli are unable to provide oxygen to this portion of the blood supply, leading to hypoxemia. Shunt physiology is due to either anatomic shunt (e.g., pulmonary embolism or arteriovenous malformation) or physiologic shunt due to alveolar filling (i.e., cardiogenic or noncardiogenic pulmonary edema) or increased flow in the alveolar–capillary beds (i.e., hepatopulmonary syndrome). A commonly encountered shunt physiology is seen with acute respiratory distress syndrome (ARDS), where the degree of shunt increases as alveolar filling worsens, causing progressively worsened hypoxemia (Table 3.1) [6].

Any of these abnormalities lead to a decrease in dissolved oxygen available in the blood or pO_2. Although dissolved oxygen plays a small role in the amount of oxygen delivered to the cell compared to hemoglobin bound oxygen, dissolved

Table 3.1 Berlin definition of ARDS

Acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (i.e., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	200 mgHg $<PaO_2/FiO_2<$300 mmHg with PEEP or CPAP >5 cmH_2O
Moderate	100 mgHg $<PaO_2/FiO_2<$200 mmHg with PEEP >5 cmH_2O
Severe	$PaO_2/FiO_2<$100 mmHg with PEEP >5 cmH_2O

oxygen is required to allow oxygen to bind hemoglobin. The clinically important etiologies of hypoxemic respiratory failure commonly encountered are as follows:

- Pneumonia
- Cardiogenic pulmonary edema
- Noncardiogenic pulmonary edema (ARDS)

Hypercapnic Respiratory Failure

Hypercapnic (Type II) respiratory failure occurs when the patient is unable to maintain blood pH by increasing minute ventilation (V_E), or the amount of CO_2 exhaled per minute determined by tidal volume multiplied by the respiratory rate [3]. CO_2 is produced in the peripheral tissues by cellular metabolism and freely dissolves across the membrane into the blood stream, unlike oxygen, which requires being bound by hemoglobin. Thus, a linear increase in CO_2 production in the periphery requires a linear increase in minute ventilation to compensate and maintain normal blood pH. Unfortunately, not all of the surface area of the respiratory system participates in gas exchange, and thus, a portion of the minute ventilation is wasted or "dead space" ventilation [7]. Dead space (V_D) occurs from an increase in conducting airways such as is seen after parenchymal loss in emphysema or in any process that leads to a relative decrease in blood supply to the alveoli such as seen in pulmonary embolism. Consequently, alveolar ventilation (V_A) is the ventilation that participates in CO_2 removal and is determined by the minute ventilation minus dead space, meaning that any increase in dead space or decrease in minute ventilation will lead to decreased alveolar ventilation causing a drop in pH [3, 7, 8]. Additionally, a relative increase in CO_2 production compared to exhaled CO_2, such as seen with metabolic acidosis, will lead to a drop in pH. Thus, pCO_2 can be expressed as follows:

$$pCO_2 = \left[VCO_2 / RR \times V_E - V_D\right] \times 0.863 \text{ or } \left[VCO_2 / V_A\right] \times 0.863$$

where VCO_2 is the production of CO_2, RR is the respiratory rate, V_E is minute ventilation, V_A is alveolar ventilation, and V_D is dead space.

Unfortunately, while pCO_2 and CO_2 production are linear, the pCO_2 response to alveolar ventilation increases in supranormal alveolar ventilation [3, 7]. The result is that while respiratory acidosis is easily compensated for by increasing alveolar ventilation, metabolic acidosis due to increased CO_2 production will often exceed the ability to compensate by increased alveolar ventilation as is often seen in lactic acidosis, diabetic ketoacidosis, and toxic ingestions.

In summary, any condition that leads to decreased respiratory drive, decreased respiratory efficiency, or increased ventilatory demand beyond the respiratory system's capacity will lead to ventilatory failure. Common conditions include the following:

- Obstructive lung diseases such as asthma or chronic obstructive pulmonary disease (COPD)
- Increased ventilatory demand from shock
- Overdoses (opiates and sedatives)

Patient Presentation

Patients with acute respiratory failure present with many different syndromes, depending on the offending gas exchange disturbance. Following are typical presentations of common causes of acute respiratory failure:

- *COPD*: Patients are typically middle age or older with a history of smoking and present with cough, dyspnea, and often chest pain. Physical exam often demonstrates barrel chest, tripoding, pursed-lip breathing, and accessory muscle use with a severely prolonged expiratory phase and wheezing.
- *Asthma*: Patients are typically younger to middle age with acute onset of wheezing, chest pain, and dyspnea. Physical examination typically demonstrates tripoding, diminished breath sounds or wheezing, and accessory

muscle use. Depending on the amount of mucous plugging, patients may have crackles and hypoxemia as well.
- *Shock*: Patients typically present with severely increased minute ventilation with tachypnea and large tidal volumes. Patients may be anxious and hypotensive. Breath sounds are typically clear.
- *Cardiogenic pulmonary edema*: Patients are typically middle age or older. If the primary cause is systolic heart failure, patients typically have ischemic cardiomyopathy either acutely or chronically. If the primary cause is diastolic heart failure, patients typically have a longstanding history of hypertension. Patients typically present with dyspnea and orthopnea. Physical examination demonstrates crackles diffusely, jugular venous distension, accessory muscle use, and a displaced point of maximal impulse.
- *Pneumonia/ARDS*: Patients often present with productive cough, chest pain, and dyspnea. They may have diminished breath sounds or crackles either locally or diffusely. As the degree of shunt increases, the oxygen saturation will become less responsive to supplemental oxygen.

Diagnostics

All patients with acute respiratory failure should have a thorough investigation into the etiology of the respiratory failure. Evaluation should include the following:

- *Evaluation for mental status changes*: If altered, mental status, medication history, and drug use should be investigated.
- *Evaluation for airspace disease*: Patients should get a chest X-ray and/or bedside ultrasound to evaluate for pulmonary edema, atelectasis, or alveolar filling processes.
- *Evaluation of gas exchange and acid–base status*: Ventilatory status can be evaluated with a venous blood gas and a metabolic panel. Oxygenation evaluation requires an arterial blood gas. With an *arterial* blood gas, the alveolar–arterial (A–a) gradient can be evaluated. With primary hypoxemic conditions (VQ mismatch, shunt, fibrosis, etc.), the A–a gradient will increase as the inspired oxygen will not diffuse into the arterial blood. With hypoxemia due to hypoventilation, the A–a gradient will be normal. When the ventilatory and acid–base status is of interest, a venous blood gas will give an accurate pH and pCO_2. However, while in healthy adults, there is a predictable correlation in pO_2 between an ABG and VBG, increased oxygen consumption, regional blood flow variation, and inconsistent pulmonary oxygenation all make a VBG unreliable in critically ill patients.
- *Evaluation of cardiovascular status*: Bedside sonographic evaluation of cardiac performance and volume status can be both diagnostic and guide therapy for cardiogenic pulmonary edema or respiratory failure due to shock.

Initial Stabilization and Treatment

Stabilization and treatment for acute respiratory failure depend on etiology (Table 3.2). Reversible causes should be sought after and treated immediately. For example, depressed respiratory drive from narcotic overdose can be easily reversed with naloxone. In general, goals with management of acute respiratory failure include the following:

- Minimize work of breathing
- Limit risk with NIPPV and risk of ventilator-induced lung injury with invasive mechanical ventilation
- Improve patient–ventilator synchrony

Ventilatory Failure from COPD or Asthma

Noninvasive positive-pressure ventilation (NIPPV) improves work of breathing and reduces symptoms, mortality, and need for intubation and mechanical ventilation compared to oxygen sup-

Table 3.2 Treatment of acute respiratory failure by diagnosis

Diagnosis	ARF type	Mechanism of ARF	NIPPV use	Indication for intubation	Ventilator mode	Monitoring	Other treatment
COPD	Hypercapnic	Increased work of breathing due to hyperinflation, decreased respiratory muscle efficiency, and dynamic hyperinflation	Decreases work of breathing, need for intubation, and mortality compared to standard therapy	pCO_2 >100 mmHg, pH <7.05, persistently high work of breathing, impending respiratory arrest, persistent hypoxemia	Volume control, low respiratory rate	Monitor expiratory flow waveform on ventilator for air trapping, follow peak pressures, and monitor blood gasses	Bronchodilators and corticosteroids
Asthma	Mixed	Bronchospasm induces hyperinflation and hypercapnia, increased work of breathing. Mucous plugging induces VQ mismatch and hypoxemia.	May reduce work of breathing, lacking outcomes data				
Cardiogenic pulmonary edema	Hypoxemia	Pulmonary edema leads to VQ mismatch, increased work of breathing	Decreases work of breathing, reduces mortality and need for intubation compared to standard therapy; improves pulmonary edema by improving hemodynamics	Persistent hypoxemia, impending respiratory or cardiac arrest, inability to tolerate mask	Volume- or pressure-targeted mode, increase PEEP, lung protective tidal volumes	Monitor blood gas for improved hypoxemia, bedside ultrasound or chest x-ray for pulmonary edema resolution, monitor tidal volumes if pressure-targeted mode, monitor pressures if volume-targeted mode	Afterload reduction and inotropic agents if necessary, intervention if active ischemia
Pneumonia ARDS	Hypoxemia	Shunt due to alveolar filling	Controversial. High failure rate, increased mortality with failure. Improved outcomes with hematologic malignancy patients	If NIPPV trial attempted, PEEP >10 and/or FiO_2 >60% and PaO_2 <100 or PF ratio <200 2 hours after initiation	Volume-targeted mode preferred, pressure-targeted mode (APRV) can improve oxygenation in refractory hypoxemia, lung protective tidal volumes necessary	Monitor blood gas for improvement in hypoxemia, monitor tidal volumes and plateau pressures (<30 cmH_2O)	Early appropriate antibiotics if infectious, steroids if inflammatory ARDS. Refractory ARDS-neuromuscular blockers, proning, inhaled NO, ECMO
Shock	Mixed	Increased work of breathing, decreased blood supply to respiratory muscles, increased CO_2 production	Unsupported	Same as above	Volume or pressure-targeted mode with lung protective tidal volumes, may need higher respiratory rate	Monitor for improvement in shock	Appropriate therapy for etiology of shock

plementation alone in patients with COPD [9–14]. NIPPV for asthma is more controversial than in COPD as there is more regional hyperinflation due to mucous plugging and flow restriction due to bronchospasm, which make the use of PEEP a risk of pneumothorax. However, NIPPV may improve work of breathing and reduce symptoms [15]. In general, keep PEEP low in asthma exacerbation requiring mechanical ventilation.

Contraindications to NIPPV in all patients include the following:

- pCO_2 >100 or pH <7.05, inability to protect airway, vomiting, hemodynamic instability, GI bleed, hemoptysis, epistaxis, excessive secretions, inability to tolerate accidental removal of NIPPV mask.
- Indications for intubation are persistently high work of breathing with evidence of fatigue, respiratory or cardiac arrest, or persistent hypoxemia.

Monitoring while on NIPPV includes blood gas with initiation of NIPPV and frequently (q1–2 hours) until stable. For COPD patients with O_2Sat >92%, a VBG can be used instead of ABG (see section "Diagnostics"). If pCO_2 is not improving or work of breathing remains high (increased RR >20, accessory muscle use), increase IPAP by 5 until 20/5. If no improvement, consider intubation and invasive mechanical ventilation.

Invasive mechanical ventilation for COPD and asthma should be performed with a volume-targeted mode (assist control (AC), synchronized intermittent mandatory ventilation (SIMV), pressure-regulated volume control (PRVC)) with a low respiratory rate (10–12 per minute). Pressure control modes must be used cautiously due to the risk of regional hyperinflation and pneumothorax.

- Decrease the respiratory rate until expiratory flow returns to baseline prior to next mandatory breath. As COPD patients have outflow obstruction, peak pressures are often high. If the peak pressure alarms, evaluate the expiratory flow waveform on the ventilator monitor for air trapping and decrease ventilator rate as needed. Allow permissive hypercapnia if necessary.
- If no air trapping is present, perform inspiratory pause to evaluate plateau pressure. If plateau pressure >30 cmH_2O, a portable X-ray or bedside ultrasound should be performed to evaluate for pneumothorax.
- If no pneumothorax is present, perform expiratory pause to evaluate autopeep. If autopeep is elevated, then increase set PEEP and decrease respiratory rate. If hypotensive, disconnect ventilator from ETT and decompress chest with external compression to allow air to empty from the lungs. Needle decompression will not allow trapped air to escape in autopeep scenarios.
- Treat bronchospasm with bronchodilators.

Hypoxemic Respiratory Failure

NIPPV improves work of breathing and reduces symptoms, mortality, and need for intubation and mechanical ventilation in patients with cardiogenic pulmonary edema [16–19]. PEEP provides the benefit in cardiogenic pulmonary edema by improving cardiac performance. However, inspiratory pressure support may be desired if high work of breathing with inspiration. Initial NIPPV settings should be EPAP (PEEP) 8–10 cmH_2O or may use IPAP of 12–15. Monitoring while on NIPPV includes blood gas prior to initiation of NIPPV and following oxygen saturation and symptoms after initiation of NIPPV. If work of breathing remains high (increased RR >20, accessory muscle use, persistent hypoxemia), titrate PEEP up to 15. If still no improvement, consider intubation and invasive mechanical ventilation.

NIPPV is in general contraindicated for hypoxemic respiratory failure due to pneumonia or ARDS given high risk of failure (50+%) [14, 20–29]. However, if NIPPV is chosen for oxygenation support, very close observation is required to monitor response to therapy. If requiring PEEP >10 and/or FiO_2 >60% and PaO_2 <100 or PF ratio <200 (i.e., moderate or severe ARDS

Table 3.3 ARDSnet PEEP/FiO_2 table for mechanical ventilation

FiO_2	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20–24

based on Berlin definition) by 2 hours after initiation, recommend intubation and mechanical ventilation [23].

Invasive mechanical ventilation for hypoxemic respiratory failure should be performed with a volume-targeted mode (assist control (AC), synchronized intermittent mandatory ventilation (SIMV), pressure-regulated volume control (PRVC)) with the following settings:

- Rate of 12–15 breaths per minute. May increase based on ventilatory requirement.
- Tidal volume of 6–8 ml/kg PBW (predicted body weight), must keep plateau pressure< 30 cmH_2O.
- Positive end-expiratory pressure (PEEP) of 5–8 cmH_2O.
- FiO_2 of 100% upon initiation and titration to SpO_2 >90.

Monitoring while undergoing mechanical ventilation should include the following:

- *Arterial* blood gas prior to intubation and q1 hour until hemodynamically stable and no active ventilator changes are needed.
- Continuous quantitative $EtCO_2$ and pulse oximetry.
- If requiring FiO_2 >60%, increase PEEP ×5 every 30 minutes until a PEEP of 15 is reached as outlined in the ARDSnet PEEP/FiO_2 table (Table 3.3) [30].
- If still persistently hypoxemic at a PEEP of 15, the patient has refractory hypoxemia.

Refractory hypoxemia (PaO_2 <60, PF <200 requiring FiO_2 >60% or PEEP ≥15 cmH_2O) is a critical problem encountered in many patients with ARDS and carries a high mortality [6, 31–33]. Many methods have been used to treat refractory hypoxemia with mixed results. At our hospital at the University of Arizona, we recommend the following therapies in ARDS patients with refractory hypoxemia.

- Consider airway pressure release ventilation (APRV mode) and adjust the high and low pressures and ensure tidal volumes are lung protective (6–8 ml/kg) as lung compliance improves [34, 35].
- Ensure adequate sedation and analgesia to minimize patient–ventilator dyssynchrony. If patient–ventilator dyssynchrony persists, consider continuous paralytic infusion [36]. Cisatracurium (Nimbex) is the preferred neuromuscular blocking agent, as it is long acting and not altered by hepatic or renal dysfunction.
- If sedation adequate and no patient–ventilator dyssynchrony, early prone positioning should be performed [37–41].
- If still persistently hypoxemic, consider inhaled nitric oxide at 10 ppm or inhaled epoprostenol (Flolan) [32].
- Discuss with intensivist colleagues if the patient is a candidate for extracorporeal membrane oxygenation (ECMO) [42].

Respiratory Failure Secondary to Shock

NIPPV is not recommended for shock-induced respiratory failure. Invasive mechanical ventilation reduces respiratory muscle oxygen consumption and diaphragm fatigue, and it reduces lung injury due to circulating cytokines and high ventilatory demand-induced volutrauma [8, 43, 44].

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