Ventilator Strategies and Rescue Therapies for Management of Acute Respiratory Failure in the Emergency Department

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Acute respiratory failure is commonly encountered in the emergency department (ED), and early treatment can have effects on long-term outcome. Noninvasive ventilation is commonly used for patients with respiratory failure and has been demonstrated to improve outcomes in acute exacerbations of chronic obstructive lung disease and congestive heart failure, but should be used carefully, if at all, in the management of asthma, pneumonia, and acute respiratory distress syndrome. Lung-protective tidal volumes should be used for all patients receiving mechanical ventilation, and FiO_2 should be reduced after intubation to achieve a goal of less than 60%. For refractory hypoxemia, new rescue therapies have emerged to help improve the oxygenation, and in some cases mortality, and should be considered in ED patients when necessary, as deferring until ICU admission may be deleterious. This review article summarizes the pathophysiology of acute respiratory failure, management options, and rescue therapies including airway pressure release ventilation, continuous neuromuscular blockade, inhaled nitric oxide, and extracorporeal membrane oxygenation. [Ann Emerg Med. 2015;■:1-13.]

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INTRODUCTION

Acute respiratory failure is commonly encountered in critically ill patients in the emergency department (ED). Annually, there are nearly 1.5 million ED visits for acute exacerbations of chronic obstructive pulmonary disease,[1] 2 million for acute asthma exacerbations,[2] more than 1 million hospitalizations for acute cardiogenic pulmonary edema,[3,4] and nearly 200,000 admissions for acute lung injury or acute respiratory distress syndrome.[5] Recently, the emergence of the H1N1 strain of influenza has led to many patients' presenting to the ED with acute respiratory distress syndrome and refractory hypoxemia.[6,7] Although acute respiratory failure is common in the ED, the expedient and proper management is both complex and critically important. A recent multicenter observation study showed that a concerning number of patients receive suboptimal mechanical ventilation while in the ED.[8] The goals of the ED management of acute respiratory failure include minimizing work of breathing, appropriately using noninvasive positive-pressure ventilation (NIPPV), improving gas exchange, optimizing patient-ventilator synchrony, and limiting risk of ventilator-induced lung injury. Controversy remains about the role of noninvasive ventilation, timing of intubation, pharmacologic and nonpharmacologic rescue therapies and their role in the ED, and the role of extracorporeal membrane oxygenation (ECMO). This review will describe the pathophysiology and state-of-the art treatment of acute respiratory failure while stressing that many of these therapies should be considered for patients in the ED rather than deferred as ICU management, particularly for boarded patients awaiting bed placement. Many of the treatment modalities highlighted present targets for high-priority research needs because they pertain to ED management of acute respiratory failure. Figure 1 summarizes the invasive and noninvasive ventilator management strategies for critically ill ED patients with acute respiratory failure.

FOUNDATIONAL CONCEPTS

Work of Breathing

The 2 goals of respiration (eliminating carbon dioxide [CO_2] and supplying oxygen) require work. Work of breathing is required by the respiratory muscles to overcome resistive and elastic forces within the lung and chest wall to move air and enable gas exchange. Resistive work of breathing is the work required to overcome resistance to airflow, whereas elastic work of breathing is that which overcomes the lung's desire to remain at functional residual capacity. The total work of breathing is the work per breath (both resistive and elastic) multiplied by the respiratory rate.

Editor's Capsule Summary

What is already known on this topic

Patients with acute respiratory failure are often initially treated in the emergency department (ED) and may require interventions commonly provided in the ICU.

What question this study addressed

This article reviews ventilatory and oxygenation failure and emphasizes physiology-based interventions in immediate management.

What this study adds to our knowledge

Acute respiratory failure treatment must minimize work of breathing and improve gas exchange while avoiding lung injury. Invasive mechanical ventilation, neuromuscular blockade, and early consultation for initiation of advanced rescue techniques are all appropriate elements of ED management.

How this is relevant to clinical practice

Emergency physicians should understand the range of treatment options for acute respiratory failure and initiate needed advanced interventions as part of a continuum of care for these often critically ill patients.

Understanding the relationships contributing to work of breathing is crucial in understanding why certain conditions lead to respiratory failure, for example, shock and chronic obstructive pulmonary disease, and may guide the types and timing of therapeutic interventions in the ED and ICU. Patients in shock have elevated work of breathing because of high ventilatory demand and resultant hyperpnea and tachypnea, which occur in the setting of decreased respiratory muscle perfusion predisposing them to diaphragm fatigue.[9-13] Mechanical ventilation can reduce this work of breathing and the high oxygen consumption required to maintain it and as a result has become a recommended therapy in shock, even in the absence of primary pulmonary pathology. In chronic obstructive pulmonary disease, work of breathing is increased by an increase in airways resistance, and also by the increased elastance caused by dynamic hyperinflation, which occurs when the inhaled tidal volume exceeds the volume that can be exhaled during expiration. This inequality of volumes leads to the development of auto–positive end-expiratory pressure (PEEP), which must then be overcome during inhalation to create the necessary pressure gradient for air to flow into the lung. Reduction of this elastic work of breathing is the mechanism for improved outcomes observed with the use of NIPPV.

Non-Invasive Positive Pressure Ventilation

Given the benefits observed with improved work of breathing and respiratory support, NIPPV use for acute respiratory failure is increasing.[14-16] The use of NIPPV is well supported in the treatment of chronic obstructive pulmonary disease exacerbations, decompensated congestive heart failure, and in immunocompromised patients.[17-26] However, current data about the use of NIPPV in acute respiratory distress syndrome and pneumonia demonstrate poor outcomes.[15,27-38] Despite evidence to avoid NIPPV in mixed respiratory failure,[15,28-30,32,37,38] NIPPV is frequently used in the ED for these conditions. In light of this evidence, a recent Agency for Healthcare Research and Quality report highlighted the lack of evidence to support NIPPV use for respiratory failure not caused by chronic obstructive pulmonary disease or congestive heart failure.[28]

Although NIPPV may decrease the need for intubation in patients with respiratory failure regardless of cause, intubation after failed NIPPV is associated with increased mortality.[14-16,26,30,32,33,36,37] Despite a reduced need for intubation and decreased mortality when NIPPV is used for acute respiratory failure as a result of chronic obstructive pulmonary disease,[15,26,36] NIPPV failure requiring intubation is associated with higher odds of mortality than in patients with chronic obstructive pulmonary disease who are intubated primarily.[14,16] Hypoxemic respiratory failure treated with NIPPV has a high failure rate, requiring intubation in 30% to 84% of cases,[15,30,37-39] and worsened mortality.[30,32] In a study of patients with hematologic malignancy and acute lung injury, NIPPV success decreased mortality, whereas NIPPV failure carried a nearly 40% higher mortality.[35] It is not clear what portion of the mortality noted with delayed intubation is attributable to initial patient selection, disease progression, or intubation-related complications.[40]

A challenge in the ED is the real-time assessment of criteria to predict the failure (or success) of a trial of NIPPV to avoid intubation. Because of diminished physiologic reserve in these critically ill patients, intubation can be particularly risky and carries a high rate of significant hypoxemia, hemodynamic deterioration, and cardiac arrest.[41-53] As such, there is interest in limiting these risks by prolonging safe apnea time or avoiding intubation altogether.[54-56] Current studies have yielded mixed results. Several studies of NIPPV for hypoxemic respiratory failure in non–chronic obstructive pulmonary disease cohorts demonstrated decreased intubation rates or mortality rates,[19-21,34,36,57,58]

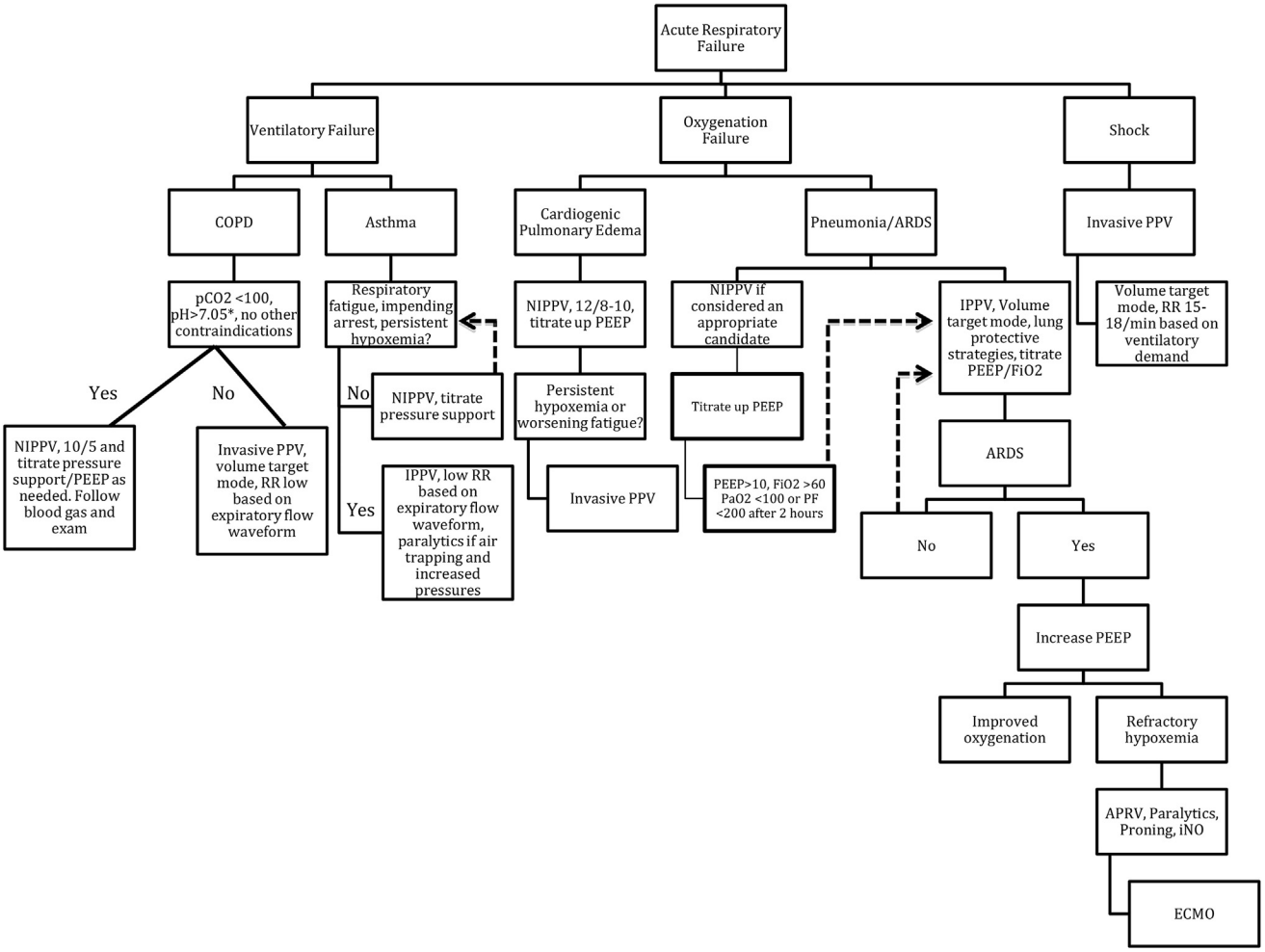

Figure 1. Invasive and noninvasive ventilator treatment strategies of respiratory failure. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that NIPPV is indicated for respiratory acidosis with a pH less than 7.35.[62,63] Sinuff et al[64] recommend NIPPV with a pH greater than 7.25, and the British Thoracic Society guidelines state NIPPV is "particularly" indicated with a pH greater than 7.25.[65] The American Thoracic Society guidelines state that for patients with a pH less than 7.25, NIPPV should be limited to the ICU for aggressive monitoring and immediate intubation if necessary.[66] In accordance with these guidelines and our clinical experience, we recommend a trial of NIPPV in the absence of contraindications for a pH greater than 7.05. *COPD*, Chronic obstructive pulmonary disease; *ARDS*, acute respiratory distress syndrome; *PPV*, positive-pressure ventilation; *RR*, respiratory rate; *PF*, PaO_2/FiO_2; *APRV*, airway pressure release ventilation; *iNO*, inhaled nitric oxide.

whereas others reported no improvement in these parameters.[31,59,60] There are some reports of success with NIPPV use for the treatment of hypoxemic respiratory failure caused by H1N1 influenza; however, there is a high failure rate requiring intubation in a substantial proportion (≈50%).[61] In multiple studies, the degree of hypoxemia and the presence of pneumonia are strongly associated with NIPPV failure.[30,61,67-70] Severe community-acquired pneumonia and acute respiratory distress syndrome have been shown to portend NIPPV failure, with a rate of more than 50%.[71,72] NIPPV can be useful for preoxygenating these patients with shunt physiology[54] before intubation and may avoid intubation altogether; however, a trial of NIPPV for hypoxemic respiratory failure longer than 1 to 2 hours without significant improvement is unlikely to be beneficial and would possibly be harmful.[29,33] Thus, the emergency physician should be mindful of patient selection, and diligent with monitoring and frequent evaluations, and should intervene early if necessary when NIPPV is used.

VENTILATORY FAILURE

Physiology

Ventilatory failure occurs when minute ventilation (minute ventilation=respiratory rate×tidal volume) is no longer adequate to remove carbon dioxide from the circulation; arterial CO_2 [$PaCO_2$]) increases and pH begins to decrease. This may be due to either hypercapnic

Table 1. Causes of hypercapnic respiratory failure.

Causes of Hypercapnia	Examples
Decreased respiratory drive	Opiate or sedative overdose
	Primary CNS injury
Neuromuscular weakness	Spinal cord injury
	Guillain-Barré syndrome
	Myasthenia gravis
	Electrolyte abnormalities
	Severe fatigue
Chest wall mechanical defect	Chest wall trauma
	Massive ascites
	Massive pleural effusion
Increased dead space ventilation	Emphysema
	ARDS
	Pulmonary embolism
Increased carbon dioxide load	Shock
	Severe sepsis
	Malignant hyperthermia

CNS, Central nervous system.

respiratory failure (type 2) or increased carbon dioxide production that outstrips ventilatory capacity, such as observed in shock (type 4 respiratory failure). Table 1 summarizes important causes of hypercapnic respiratory failure.

A portion of every breath, known as dead space, never reaches the alveolar-capillary interface and thus does not participate in gas exchange.[73] Increased dead space occurs from any volume increase in conducting airways (eg, emphysema) or a relative decrease in blood supply to the alveoli (eg, pulmonary embolism). Thus, only alveolar ventilation (alveolar ventilation=[minute ventilation–dead space]) participates in carbon dioxide removal, and any increase in dead space or decrease in minute ventilation will lead to decreased alveolar ventilation and a decrease in pH.[11]

Unlike oxygen, which is mostly transported bound to hemoglobin, carbon dioxide produced in the periphery freely dissolves across cell membranes into the blood. Thus, for any increase in carbon dioxide production without a change in alveolar ventilation, there is an equivalent increase in $PaCO_2$. With an increase in carbon dioxide production, there must be an increase in alveolar ventilation to maintain a neutral pH. Yet, although the relationship between carbon dioxide production and $PaCO_2$ is linear, the relationship between $PaCO_2$ and alveolar ventilation is not. At normal alveolar ventilation and below, the relationship is linear, meaning that respiratory acidosis can be improved by increasing alveolar ventilation in the same proportion. However, at supranormal ranges of alveolar ventilation, carbon dioxide removal plateaus, such that severe metabolic acidosis can result in a respiratory compensation requirement that cannot be met by increasing alveolar ventilation.[73,74]

Recommendations for Emergency Department Management

Patients with ventilatory failure as a result of chronic obstructive pulmonary disease or asthma can receive a trial of NIPPV in the absence of contraindications, which include inability to protect the airway, vomiting, hemodynamic instability, excessive secretions, or inability to tolerate accidental removal of NIPPV mask.[75] NIPPV improves work of breathing, improves symptoms, reduces mortality, and lessens the need for intubation compared with oxygen supplementation alone in patients with chronic obstructive pulmonary disease. However, NIPPV for asthma is more controversial and less rigorously studied. NIPPV may reduce work of breathing and symptoms in severe asthma, but regional hyperinflation caused by mucous plugging and flow restriction caused by bronchospasm in asthma increases the potential of pneumothorax. Monitoring while the patient receives NIPPV includes blood gas analysis with initiation of NIPPV and frequently (every 1 to 2 hours) until stable. For patients with chronic obstructive pulmonary disease without hypoxemia, a venous blood gas can be used instead of an arterial blood gas. If the PCO_2 is not improving or work of breathing remains high (tachypnea or accessory muscle use), the inspiratory pressure support should be increased by 5 cm H_2O until 20 cm H_2O/5 cm H_2O. Indications for intubation include persistently high work of breathing with evidence of fatigue or impending respiratory or cardiac arrest, persistent hypoxemia, and failure to improve while receiving NIPPV.

Invasive mechanical ventilation for chronic obstructive pulmonary disease and asthma can be performed with either a pressure- or volume-targeted mode. The critical actions are to limit mean airway pressures and minute ventilation to limit air trapping while allowing permissive hypercapnia as long as the pH remains above 7.20 and the patient is hemodynamically stable. For the emergency physician, this may be easiest with a volume-targeted mode (ie, assist control or pressure-regulated volume control) with a low respiratory rate (10 to 12 breaths/min) and may require a neuromuscular blocker. The respiratory rate should be decreased until the expiratory flow waveform returns to baseline before the next breath. If the peak pressure alarms, evaluate the expiratory flow waveform for air trapping and increase expiratory time by decreasing the ventilator respiratory rate as needed (Figure 2). If no air trapping is present, perform an inspiratory pause to evaluate plateau pressure. If the plateau pressure is greater than 30 cm H_2O, a portable radiograph or bedside ultrasound should be performed to evaluate for pneumothorax. If no pneumothorax is

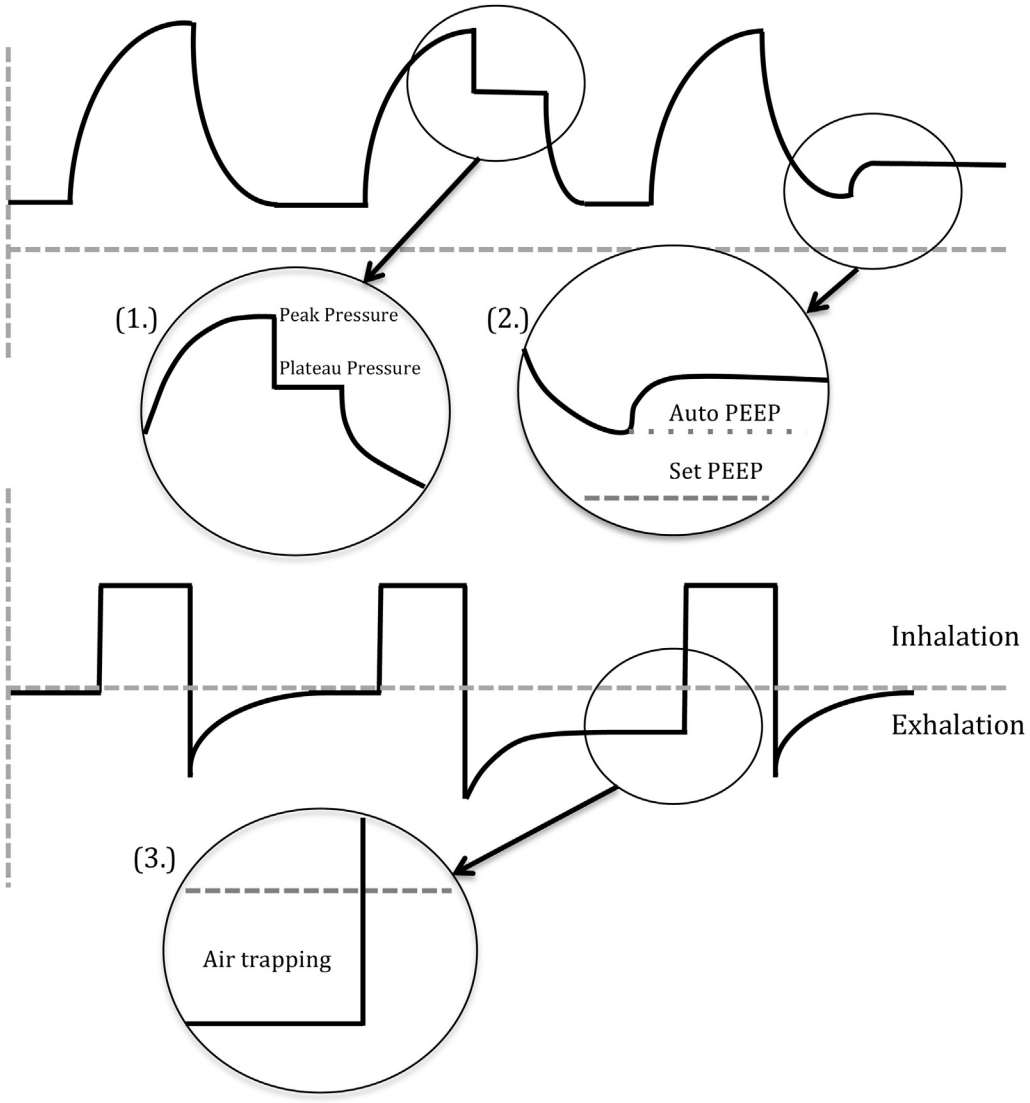

Figure 2. Expiratory flow, inspiratory, and expiratory holds for air trapping and auto-PEEP. Pressure (upper) and flow (lower) ventilator waveforms during 3 consecutive breaths. An inspiratory hold maneuver (1) on the ventilator will stop all flow after inspiration, isolating the pressure at the alveolar level known as plateau pressure. An expiratory hold maneuver (2) will inhibit inspiration and measure the end-expiratory pressure in the respiratory system. Any elevation of the total PEEP above the set PEEP is due to auto-PEEP. The flow waveform (lower) is useful for evaluating air trapping. After the first breath, the expiratory flow limb returns to baseline before the next breath. After the second breath, the expiratory flow limb fails to return to baseline before the next breath, leading to air trapping (3), as is commonly observed in obstructive lung disease such as asthma and chronic obstructive lung disease.

present, perform an expiratory pause to evaluate auto-PEEP. If auto-PEEP is elevated, then decrease the respiratory rate, increase the inspiratory flow to lengthen the expiratory time, or, in the case of chronic obstructive pulmonary disease, increase set PEEP to 80% of the total PEEP (set PEEP plus auto-PEEP) to assist respiratory muscles in overcoming the auto-PEEP (Figure 2). If the patient is hypotensive, disconnect the ventilator from the endotracheal tube and externally compress the chest to facilitate exhalation.

Given the modern focus on lung-protective ventilation with low tidal volumes, manipulation of the respiratory rate has become the primary means of adjusting ventilation. As respiratory rate increases, the proportion of time spent in exhalation decreases. In this way, rapid respiratory rates increase the risk of dynamic hyperinflation, in which more air enters during inspiration than leaves in expiration. This condition results in progressively higher intrathoracic pressures, elevated peak and plateau pressures, an increase in inspiratory threshold pressure required to trigger the

ventilator, and ultimately hemodynamic compromise as intrathoracic pressure impairs venous return to the heart. In certain circumstances, such as acute respiratory distress syndrome and obstructive lung disease, efforts to maintain eucapnia should be abandoned because attempts to normalize ventilation may be damaging. This paradigm is known as permissive hypercapnia, and the associated acidemia is well tolerated down to at least a pH of 7.2, with the exception of only a few types of patients (Figure 3).[76] In special circumstances, the utmost effort must be made to satisfy ventilatory demands, such as in the case of severe metabolic acidosis (eg, diabetic ketoacidosis, salicylate toxicity), to prevent loss of respiratory compensation and cardiovascular collapse associated with a sudden decrease in an already severely low pH. In these cases, an interesting consideration is that even abandoning low tidal volume ventilation and setting the respiratory rate as high as the ventilator will allow may still be insufficient to match the patient's preintubation minute ventilation. Pressure support (or "spontaneous") mode ventilation with adequate pressure support may be a useful alternative in the nonparalyzed patient in these instances.

OXYGENATION FAILURE

Physiology

Hypoxemic (type 1) respiratory failure occurs from any disturbance that leads to a decrease in dissolved oxygen available in arterial blood (PaO_2), which is required for hemoglobin to bind oxygen for delivery to the cells. There are 6 pathophysiologic mechanisms that lead to hypoxemia (Table 2). The more common, clinically significant causes of hypoxemic respiratory failure are ventilation-perfusion (VQ) mismatch and shunt. Hypoxemia caused by hypoventilation is a result of increased partial pressure of carbon dioxide (PCO_2) in the alveolar space displacing oxygen.[12] Diffusion abnormalities, such as interstitial lung disease, typically cause clinically significant hypoxemia only in increased demand states, such as high cardiac output.[74]

- Severe left- or right-sided ventricular failure
- Pulmonary hypertension
- Intracranial hemorrhage or concern for elevated intracranial pressure
- Salicylate or sodium-channel blocking (eg, tricyclic antidepressant) overdose
- Pregnancy

Figure 3. Contraindications to permissive hypercapnia.

Table 2. Causes of hypoxemia.

Causes of Hypoxemia	Examples
VQ mismatch	Pneumonia
	ARDS
	Pulmonary embolism
	Cardiogenic pulmonary edema
Shunt physiology	Severe ARDS
	Hepatopulmonary syndrome
	Arteriovenous malformation
	Intracardiac right-to-left shunt
Low available inspired oxygen	High altitude
	Scuba-diving mishap
	Combustion within a closed space
Hypoventilation	Opiate overdose
	COPD
	Neuromuscular disease
	Chest wall rigidity
	Upper airway obstruction
Diffusion defect	Interstitial lung disease
Low mixed venous oxygen	Severe shock

Decreased FiO_2 as a cause of hypoxemia is often a misnomer that refers to a decrease in the partial pressure of oxygen observed at high elevations because of barometric pressure limitations on alveolar gases, given fixed fractions of inspired oxygen, nitrogen, and water vapor.[77] True decreased FiO_2 is exceptionally rare in the health care setting and typically occurs in enclosed airtight spaces such as spaceships or submarines, scuba-diving misadventures, or massive fires where oxygen is rapidly consumed.

VQ mismatch, disruption of the optimal ratio of alveolar ventilation to alveolar perfusion, leads to either underperfused or underventilated alveoli (Figure 4). A high VQ ratio occurs with underperfused alveoli relative to ventilation and results in dead space ventilation, frequently observed in chronic obstructive pulmonary disease as emphysematous changes lead to parenchymal loss. A low VQ ratio, or shunt physiology, occurs when perfused alveolar units do not participate in gas exchange. Shunt physiology may be either anatomic (eg, arteriovenous malformation, intracardiac right-to-left shunting) or physiologic because of alveolar filling (eg, cardiogenic or noncardiogenic pulmonary edema) or increased flow in the alveolar capillary bed (eg, hepatopulmonary syndrome). In severe shock states with oxygen delivery-demand mismatch, a low mixed venous oxygen saturation from low cardiac output or high peripheral extraction can worsen arterial hypoxemia in the presence of shunt physiology (eg, acute respiratory distress syndrome).[78]

Acute respiratory distress syndrome is a life-threatening cause of hypoxemic respiratory failure resulting from either direct or indirect lung injury and represents a severe form of VQ mismatch commonly encountered in the ED, as exudative alveolar filling may lead to critical shunt

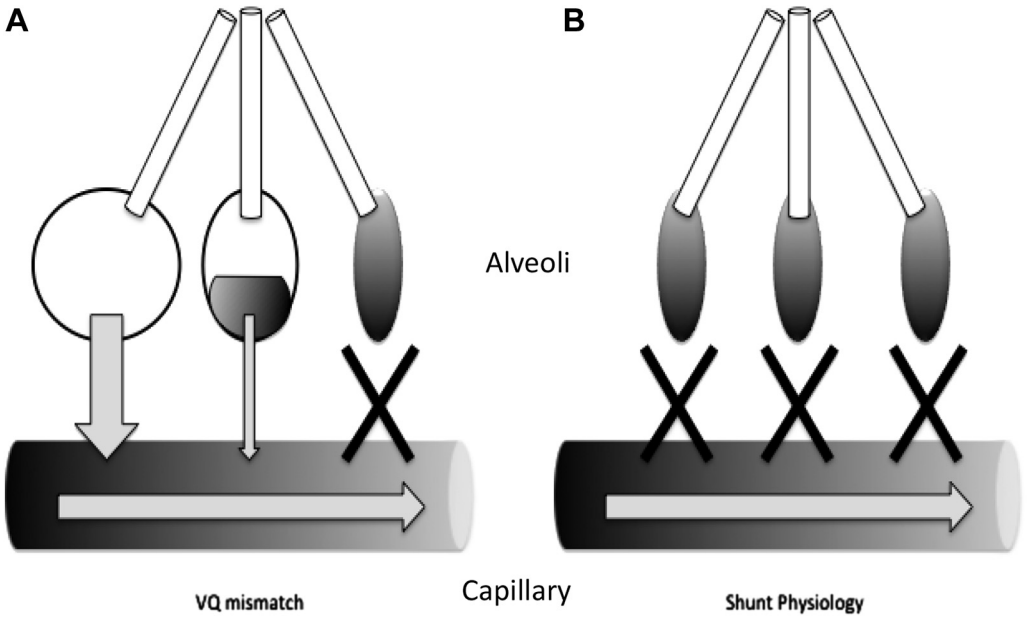

Figure 4. VQ mismatch versus shunt in ARDS. *A*, VQ mismatch occurs with regional differences in the optimal alveolar-capillary interface as gas exchange occurs unimpeded (wide arrow) in some areas and restricted (narrow arrow) or prohibited (X) in others. This mismatch can cause dead space when blood flow to well-ventilated alveoli is inhibited and areas of shunt where there is alveolar filling or parenchymal loss; both are observed in patients with COPD who improve their VQ matching by hypoxic vasoconstriction. *B*, Shunt occurs when blood flow does not participate in gas exchange, such as is observed with ARDS.

physiology.[27,79] It was first identified in the early 1800s and described in 1967,[80] but it was not until 1994 that the syndrome was formally defined to coordinate research and epidemiologic efforts.[27] The multisociety-sponsored ARDS Definition Task Force convened in 2012 and published the Berlin Definition of acute respiratory distress syndrome in an attempt to increase precision of the diagnosis (Table 3).[79] Under the Berlin Definition, nearly 80% of patients with acute respiratory distress syndrome have profound oxygenation deficits (50% moderate, 28% severe), which is associated with a high mortality (32% for moderate, 45% for severe).[79]

Table 3. Berlin Definition of acute respiratory distress syndrome.[79]

Timing	Within 1 wk 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 (ie, echocardiography) to exclude hydrostatic edema if no risk factor present.
Oxygenation	
Mild	200 mg Hg<PaO_2/FiO_2<300 mm Hg with PEEP or CPAP >5 cm H_2O
Moderate	100 mg Hg<PaO_2/FiO_2<200 mm Hg with PEEP >5 cm H_2O
Severe	PaO_2/FiO_2 <100 mm Hg with PEEP >5 cm H_2O

Additionally, nearly a third of patients with mild acute respiratory distress syndrome progress to either moderate or severe disease within a week, increasing the mortality to nearly 50%.

The management of patients with acute respiratory distress syndrome is challenging, and most patients require mechanical ventilation. The alveolar filling process leads to an oxygenation defect that leaves relatively uninvolved portions of the lung responsible for performing gas exchange. With inspiration, the volume will be heterogeneously distributed, with the uninvolved high-compliance regions of the lung receiving a higher proportion of the volume. This heterogeneous distribution leads to a cycle of overdistention and collapse, causing ventilator-induced lung injury, further perpetuating acute respiratory distress syndrome, systemic inflammation, multiorgan failure, and death. As such, lung-protective ventilation using low tidal volumes (6 mL/kg predicted body weight), limiting plateau pressures (<30 cm H_2O), and avoiding oxygen toxicity (FiO_2 <0.6) by the application of PEEP has become the standard of care and is important for preventing acute respiratory distress syndrome in patients intubated for acute respiratory failure.[81,82] However, despite some success with these interventions, the mortality remains high. Consequently, there has been increased interest in rescue therapies to improve oxygenation and mortality in severe acute respiratory distress syndrome.

Rescue Oxygenation Strategies in Acute Respiratory Distress Syndrome

Airway pressure release ventilation is an increasingly popular ventilator mode aimed at improving oxygenation in patients with severe airspace disease. It maintains a high airway pressure (eg, 30 cm H_2O for 3 to 4 seconds), periodically releasing the pressure to a set PEEP for a short duration (eg, 10 cm H_2O for 0.5 to 1 second) to allow ventilation. In this way, it is similar to inverse ratio pressure control ventilation in improving alveolar recruitment by increasing the mean airway pressure through spending a greater proportion of the breath in inspiration. The benefits of airway pressure release ventilation are the ability to maintain spontaneous breathing and improve alveolar recruitment. The risk of airway pressure release ventilation, as with any pressure-targeted mode, is injurious tidal volumes as lung compliance changes. As compliance improves with resolving disease, tidal volumes may increase, exceeding lung-protective volumes and resulting in volutrauma. Similarly, tidal volumes will decrease in the presence of worsening compliance and result in ineffective ventilation. For this reason, tidal volumes in patients receiving pressure-targeted modes such as airway pressure release ventilation must be closely monitored. Airway pressure release ventilation has been beneficial in patients with acute respiratory distress syndrome from H1N1 and has been shown to prevent the development of acute respiratory distress syndrome in high-risk trauma patients.[7,83-88]

Continuous neuromuscular blockade has been proposed as an adjunct therapy in acute respiratory distress syndrome to improve patient-ventilator synchrony and chest wall compliance, and to reduce ventilator-induced lung injury. A large-scale randomized controlled trial of early continuous neuromuscular blockade for 48 hours demonstrated a mortality and duration of mechanical ventilation benefit compared with that of a control group.[89] Continuous neuromuscular blockade is not without risks, including development of critical illness myopathy and high sedative requirements, leading to delirium and long-term cognitive abnormalities.[90-93]

Inhaled nitric oxide is a pulmonary vasodilator that is delivered to the well-ventilated portions of the lung and dilates the surrounding vasculature, improving VQ matching and oxygenation. Although it has been shown to improve oxygenation[94] and reduce oxidative stress,[95,96] it has not been shown to improve mortality in patients with acute respiratory distress syndrome, regardless of severity.[97]

Prone positioning is a nonpharmacologic method of improving oxygenation in patients with severe acute respiratory distress syndrome. This facedown positioning improves VQ match by decreasing dependent atelectasis and has improved oxygenation and mortality in patients with severe acute respiratory distress syndrome.[98-102] Prone positioning can be performed on a standard hospital bed without special equipment, but drawbacks include making routine nursing tasks and procedures more challenging.

ECMO is a method of mechanically supporting systemic oxygenation or cardiac output by removing venous blood from a large cannula in a central vein, oxygenating and removing carbon dioxide with a membrane lung, and returning that oxygenated blood to the circulation. ECMO in severe acute respiratory distress syndrome allows lung-protective ventilation by allowing rest ventilator settings and externally controlling gas exchange.[103] Although previous trials had negative results, recent improvements in membrane technology and catheter systems have led to renewed interest.[104] A multicenter randomized controlled trial showed benefit in patients referred to an ECMO center for "consideration of ECMO" compared with standard therapy at the referring center.[105] Moreover, ECMO has been successfully used for rescue therapy in patients with severe acute respiratory distress syndrome caused by pandemic influenza.[106,107] Although ECMO allows extracorporeal gas exchange and lung-protective ventilation, cannulation commonly leads to a systemic inflammatory response because of cytokine release, requires anticoagulation, has bleeding complications, requires intensive nursing, and typically leads to long ICU stays. A randomized controlled trial (the EOLIA Trial) is currently under way, investigating early ECMO initiation after 3 to 6 hours of optimal ventilator and adjunct therapy. ECMO may be a useful rescue therapy in facilities with equipment, intensivists, and surgeons skilled in the cannulation and management of ECMO patients.[104,108] For emergency physicians, it will be critical to better define which patients would benefit from ECMO for optimal timing and referral to ECMO-capable units.

Recommendations for Emergency Department Management

The management of oxygenation failure depends on the etiology. NIPPV improves work of breathing and reduces symptoms, mortality, and need for intubation and mechanical ventilation in patients with cardiogenic pulmonary edema.[23] PEEP provides benefit in cardiogenic pulmonary edema by improving left ventricular performance. However, inspiratory pressure support may be desired if the patient has high work of breathing with inspiration. Initial NIPPV settings should be positive end-expiratory pressure (PEEP) 8 to 10 cm H_2O and, if used, an inspiratory pressure support of 12 to 15 cm

H_2O. If work of breathing remains high (tachypnea or accessory muscle use) or there is persistent hypoxemia, titrate PEEP up to 15 cm H_2O. If no improvement is noted, consider intubation. If NIPPV is used for hypoxemic respiratory failure caused by pneumonia or acute respiratory distress syndrome, it should be used cautiously, given the high risk of failure and poor outcomes in patients who fail treatment; and very close observation is required to monitor response to therapy. If requiring PEEP greater than 10 cm H_2O or FiO_2 greater than 0.60, and PaO_2 <100 mm Hg or PaO_2:FiO_2 ratio less than 200 (ie, moderate or severe acute respiratory distress syndrome according to the Berlin Definition) by 2 hours after initiation, intubation and mechanical ventilation is recommended.

Invasive mechanical ventilation for hypoxemic respiratory failure should be performed with a volume-targeted mode (assist control, synchronized intermittent mandatory ventilation, or pressure-regulated volume control), with the following initial settings: rate of 12 to 15 breaths/min or more in the absence of auto-PEEP (or higher in the face of high ventilatory demand such as in severe metabolic acidosis), tidal volume of 6 mL/kg predicted body weight, PEEP of 5 to 8 cm H_2O, and FiO_2 of 100% on initiation, with a rapid wean using pulse oximetry to a goal FiO_2 less than 60% to prevent oxygen toxicity. If requiring FiO_2 greater than 60%, increase PEEP by 5 cm H_2O every 30 minutes, as outlined in the ARDSnet PEEP/FiO_2 table (Table 4).[109] If the patient is still persistently hypoxemic at a PEEP of 15 cm H_2O, treat as refractory hypoxemia.

Refractory hypoxemia (PaO_2 <60 mm Hg, PaO_2/FiO_2 <200 despite FiO_2 >60% or PEEP ≥15 cm H_2O) is a critical problem encountered in many patients with acute respiratory distress syndrome and carries a high mortality. Many methods have been used to treat it, although supporting data are mixed. We recommend the following therapies in patients with acute respiratory distress syndrome with refractory hypoxemia:

- Consider airway pressure release ventilation, adjusting the high and low pressures as compliance improves to ensure lung-protective tidal volumes (predicted body weight 6 mL/kg).
- Optimize sedation and analgesia to minimize patient-ventilator dyssynchrony. If dyssynchrony persists despite optimal sedation and attempts to optimize patient comfort with the ventilator such as providing adequate inspiratory flow, consider continuous neuromuscular-blocking agent infusion. Cisatracurium (Nimbex) is the preferred neuromuscular-blocking agent because it is eliminated by Hofmann degradation and thus does not need dosing adjustment in renal or hepatic insufficiency. This intervention has been demonstrated to improve mortality.
- Early prone positioning should be considered to improve alveolar recruitment and zone 2 ventilation. This intervention has been demonstrated to improve mortality.
- Inhaled nitric oxide at 10 parts per million can be considered to improve VQ matching and oxygenation, although this has not been convincingly demonstrated to improve patient mortality.
- Discuss with intensivist colleagues whether the patient is a candidate for ECMO. Precise indications for this therapy have yet to be well established.

CONCLUSION

Acute respiratory failure is a commonly encountered emergency that is identified in 2 forms, type 1, or hypoxemic respiratory failure, and type 2, or hypercapnic respiratory failure. Work (energy) is required to accomplish both oxygenation and ventilation, the 2 primary goals of respiration. Work of breathing is determined by respiratory rate, resistance to airflow, and the elastance of the respiratory system. NIPPV has been demonstrated to improve outcomes in acute exacerbations of chronic obstructive pulmonary disease and congestive heart failure; however, it should be used carefully, if at all, in the management of asthma, pneumonia, and acute respiratory distress syndrome. Invasive mechanical ventilation should generally be initiated

Table 4. ARDSnet PEEP/FiO_2 tables.

A, Low PEEP.														
FiO_2	0.30	0.40	0.40	0.50	0.50	0.60	0.70	0.70	0.70	0.80	0.90	0.90	0.90	1.0
PEEP, cm H_2O	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
B, High PEEP,														
FiO_2	0.30		0.30	0.40	0.40		0.50	0.50	0.50–0.80		0.80		0.90	1.0
PEEP, cm H_2O	12		14	14	16		16	18	20		22		22	22–24

Above are FiO_2 and PEEP levels suggested by the ARDSnet investigators for achieving lung-protective ventilation. For example, a patient requiring 80% FiO_2 has a suggested PEEP of 14 according to the low-PEEP table and 20 to 22 according to the high-PEEP table. Clinical outcomes were similar between higher and lower PEEP assignments[109]; however, in patients with refractory hypoxemia, use of the high-PEEP table may improve oxygenation.

with a volume control mode in the ED. Lung-protective tidal volumes based on ideal body weight should be provided even in the absence of acute respiratory distress syndrome, and FiO_2 should be reduced shortly after intubation to achieve a goal of less than 60%. In the setting of ventilatory failure caused by chronic obstructive pulmonary disease or asthma, goals of invasive mechanical ventilation are to limit mean airway pressures, increase expiratory time, and, for chronic obstructive pulmonary disease, augment set PEEP to improve work of breathing. In cases of refractory hypoxemia, emergency physicians should consider rescue therapies such as airway pressure release ventilation, neuromuscular blockade, prone positioning, and inhaled nitric oxide; finally, consultation for consideration of ECMO may be appropriate. Consideration of these therapies provides important research questions for the emergency physician, such as (1) which patients are more likely to be successfully treated with NIPPV?; (2) in hypoxemic respiratory failure, which patients are mostly likely to benefit and what is the optimal timing and order of the rescue therapies available such as neuromuscular blockade, inhaled nitric oxide, and airway pressure release ventilation?; and (3) which patients would benefit and what is the optimal timing of ECMO initiation for severe acute respiratory distress syndrome with refractory hypoxemia?

The management of acute respiratory failure is a critical and common aspect of emergency medicine. A keen understanding of the underlying pathophysiology will serve the emergency physician well in the management of acute respiratory failure.

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