CME

Acute respiratory distress syndrome

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a severe, often fatal, lung condition frequently seen in patients in the ICU. ARDS is triggered by an inciting event such as pneumonia or sepsis, which is followed by an inappropriate host inflammatory response that results in pulmonary edema and impaired gas exchange, and may progress to fibrosis. With the increased spotlight and discussion focused on ARDS during the COVID-19 pandemic, healthcare providers must be able to identify and manage symptoms based on evidence-based research.

Keywords: acute respiratory distress syndrome, ARDS, COVID-19, pneumonia, prone, Berlin criteria

Learning objectives

- Identify the most common predisposing risk factors for ARDS.
- Recognize the diagnosis of ARDS based on the Berlin criteria and exclusion of other causes.
- Incorporate evidence-based respiratory and supportive therapies to manage patients with ARDS.

ARDS was first described more than 50 years ago and has since been recognized as one of the most common diseases in patients in the ICU, with an exceptionally high mortality.[1] ARDS places a significant burden on ICUs, contributing to about 10% of all ICU admissions and 23% of all patients requiring mechanical ventilation during hospital admission.[1] ARDS has been extensively researched over the years because of its high prevalence. In 1994, the ARDS Network (ARDSNet) was established to create protocols and guidelines for treating ARDS.

Although much has been learned about this disease and its management, ARDS still carries a significant mortality, which correlates to severity of disease.[1] Inhospital mortality for mild, moderate, and severe disease was about 35%, 40%, and 46%, respectively in 2014.[1] Because ARDS is a significant complication of COVID-19 infection, discussion of ARDS management has returned to the spotlight with increased appreciation of its pervasiveness in the ICU, its complexity, and its lethality.

PATHOPHYSIOLOGY

ARDS is a form of severe lung injury that develops after an insult (pulmonary or extrapulmonary) to the body. Pneumonia accounts for 35% to 50% of cases; sepsis, 30%; aspiration, 10%; and trauma, 10%.[2] Other insults such as transfusion reactions and surgeries have been observed.[3,4] There have been very few cases in which no inciting insult has been identified.[2]

The pathogenesis of ARDS begins with an inappropriate host inflammatory response to an inciting event, causing damage to the alveolar endothelium. This results in porous membranes that inhibit appropriate gas exchange between the pulmonary vasculature and the alveoli. However, this process appears to be more complicated than initially thought. The epithelium of normal, healthy alveoli is semipermeable to allow for homeostasis of hydrostatic and oncotic pressures, which promotes exchange of oxygen and carbon dioxide. In ARDS, this system is disrupted by an inappropriate inflammatory response (**Figure 1**).

Although multiple mechanisms likely contribute to the pathological cascade of events, the best understood mechanism involves the activation of neutrophils. When neutrophils are triggered, an inflammatory cascade is initiated, releasing cytokines, procoagulant molecules, oxidants, proteases, and other toxic mediators. These toxic metabolites cause damage to the lung endothelium and alveolar epithelium, which degrades the integrity of their semipermeable membranes. These damaged membranes become porous, allowing proteins to cross into the interstitium, altering the oncotic pressures and, therefore, increasing interstitial fluid.[5] The development of protein-dense pulmonary edema and alveolar inflammation impairs gas exchange and decreases lung compliance. This catastrophic cascade also contributes to endothelial dysfunction, induction of pulmonary vasoconstriction, formation of microvascular emboli, and potential vascular remodeling, resulting in pulmonary hypertension.[6]

The progression of ARDS is staged based on pathological findings and divided into acute, subacute, and chronic phases. Although staging is based on histological samples

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Key points

- Corticosteroids are indicated for patients with severe ARDS.
- Conservative fluid management reduces the number of days patients are on the ventilator and in the ICU.
- Early prone positioning for at least 16 consecutive hours reduces patient mortality.
- Most patients will require mechanical ventilation.
- ARDSNet guidelines recommend lung-protective ventilation with low tidal volumes (6 to 8 mL/kg of ideal body weight) and peak pressures below 30 cm H_2O.

which are not commonly obtained, understanding of the progression and clinical context can be used to assess disease progression. The *acute phase*, also known as the exudative stage, is present within the first 6 days of disease, and characterized by pulmonary edema and endothelial and epithelial damage. Days 7 through 14 correlate with the *subacute phase*, also known as the fibroproliferative stage, in which edema improves and epithelial repair with collagen and fibroblasts begins. The *chronic phase*, also known as the fibrotic stage, typically occurs after 14 days and is characterized by clearance of acute neutrophilic infiltration with residual fibrosis. Not all patients progress to fibrosis and in some, ARDS resolves without residual lung damage.[5]

DIAGNOSIS

ARDS typically is a clinical diagnosis based on patient history and exclusion of other possible causes. Patients commonly present with hypoxemia and normal or nonspecific chest radiograph findings of bilateral opacifications, leaving a wide differential diagnosis. Most specifically, cardiogenic pulmonary edema can present very similarly in terms of symptoms and chest radiograph findings. If other possible differential diagnoses are either ruled out or of low suspicion, then ARDS can be diagnosed based on the Berlin criteria:

- Presentation within 1 week of clinical insult
- Bilateral opacification on chest radiograph
- Symptoms that are not better explained to be cardiac in origin
- PaO_2/FiO_2 less than 300 mm Hg.[7]

Staging of severity is based on the PaO_2/FiO_2 ratio (P:F), with mild disease defined as 200 to 300 mm Hg, moderate

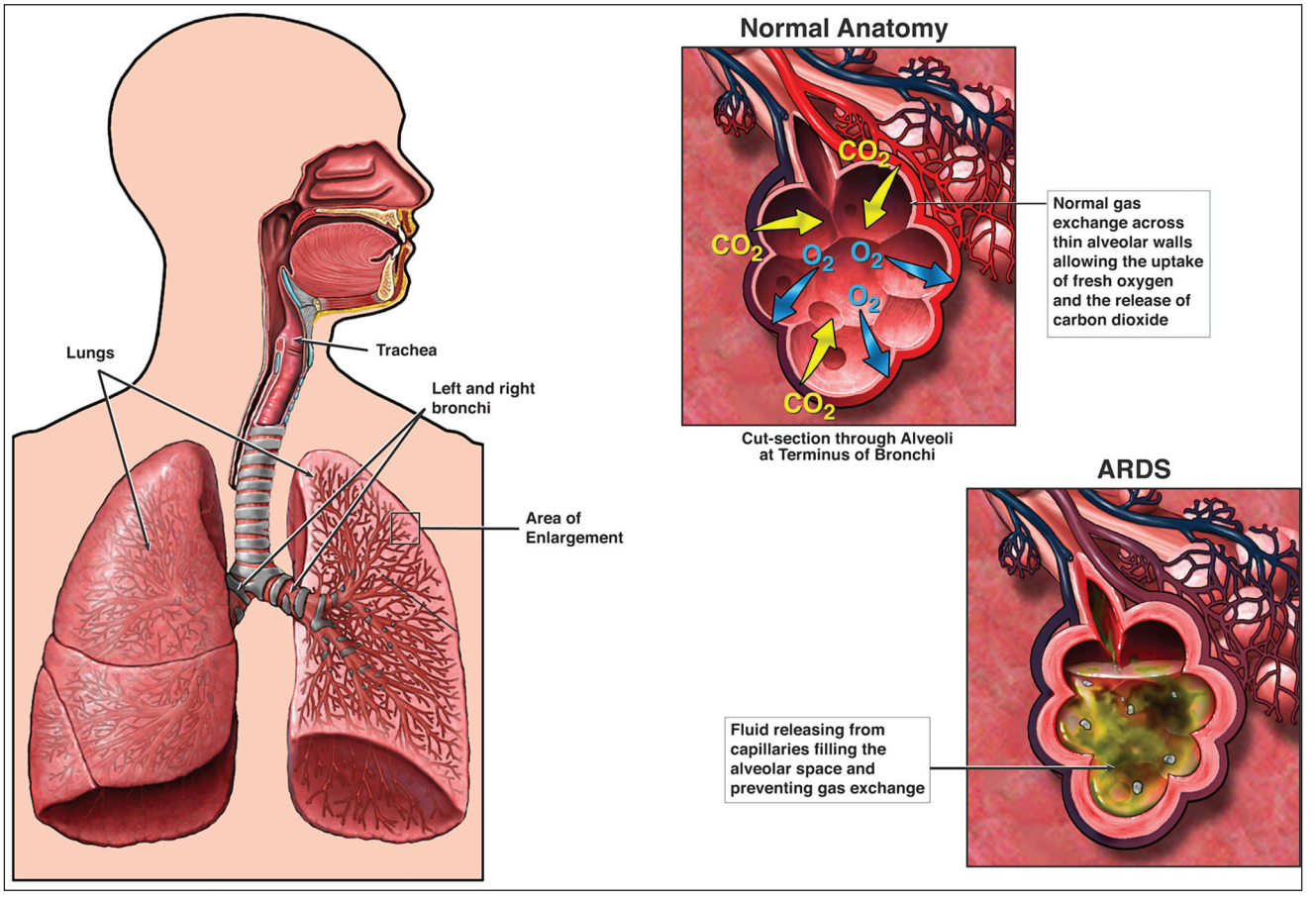

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FIGURE 1. Mechanism of ARDS

disease as 100 to 200 mm Hg, and severe disease as less than 100 mm Hg.[7] Positive end-expiratory pressure (PEEP) may affect the specificity and reliability of P:F, altering its utility as a diagnostic calculation. Therefore, the above staging is only applicable to patients mechanically ventilated on at least 5 cm H_2O of PEEP.[7]

Patients with a low P:F ratio require high FiO_2 settings secondary to their decreased ability to absorb oxygen. In addition to hypoxemia seen on arterial blood gases, patients also typically have hypercarbia. Just as oxygen absorption is impaired, the damaged alveoli and vascular epithelium struggle to expel carbon dioxide, resulting in respiratory acidosis.

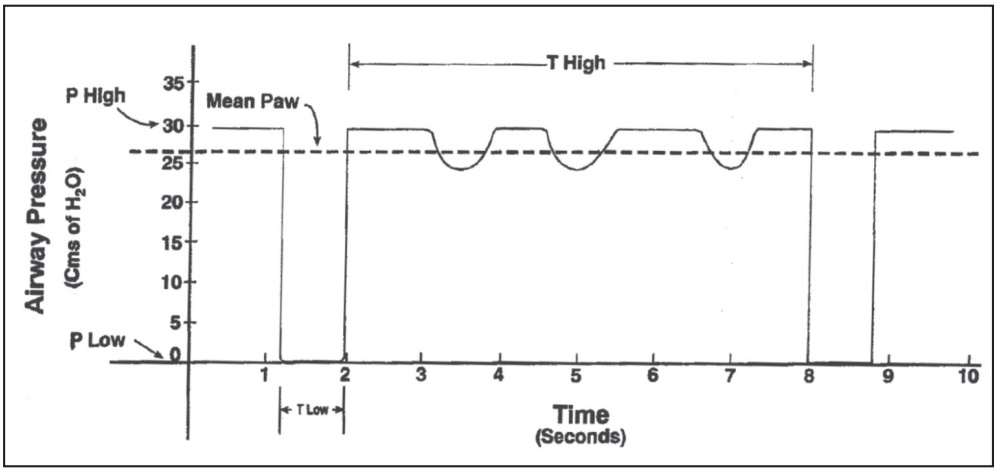

FIGURE 2. APRV waveform
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MANAGEMENT

The best evidence for reduction of mortality in ARDS management centers on prone positioning and mechanical ventilation, but other supportive measures such as glucocorticoids, conservative fluid management, and respiratory support with noninvasive ventilation (NIV) are widely used. If possible, treat the inciting event.

Prone positioning has recently gained the spotlight in the supportive management of patients with COVID-19, but studies demonstrating its effectiveness were published years before the pandemic began. Proning was an underused practice in many hospitals before the COVID-19 pandemic, likely because of its logistic complexity and clinicians' overall lack of experience with managing a prone patient. Early prone positioning for at least 16 consecutive hours has been proven to reduce mortality rates in patients with severe ARDS and P:F less than 150 mm Hg, and is presumed to be more effective in more severe disease.[8] Prone positioning is believed to improve ventilation-perfusion matching with less gravity-dependent atelectasis, help secretions drain, and reduce ventilator-induced lung injury.[8] Recent studies evaluating COVID-19 and prone positioning describe improvement in P:F for patients on noninvasive ventilation and reduced mortality for those mechanically ventilated.[9,10] Complications of prone positioning include pressure ulcers, dependent edema specifically of the face, and dislodgement of endotracheal and invasive tubing.[8]

Although noninvasive ventilation measures such as standard nasal cannula, heated high-flow nasal cannula, and bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP) may be satisfactory for management of mild disease, many patients with ARDS ultimately require mechanical ventilation. The ARDSNet protocol supports lung-protective ventilation with low tidal volumes of 6 mL/kg of ideal body weight with allowance up to 8 mL/kg if necessary, as long as plateau pressures remain less than 30 cm H_2O. This method of mechanical ventilation has been proven to reduce mortality and increase ventilator-free days.[11] Plateau pressures are measured during a held inspiration and represent the pressure seen on the alveolar level when flow resistance is absent. Maintaining peak plateau pressures below 30 cm H_2O is important in patients with ARDS to reduce barotrauma—excessive stretching and rupture of alveoli caused by high pressure gradients between the alveoli and interstitial space. ARDSNet also created PEEP-to-FiO_2 guidelines as part of its ventilator protocol.[12]

These ventilation goals can be achieved with either pressure control or volume control modes. Pressure control uses variable tidal volume to reach a set pressure. This generally is considered more lung-protective than volume control ventilation and the superior method for alveolar recruitment. On the other hand, volume-control ventilation settings apply various pressures to achieve a set tidal volume. Disadvantages to volume-control mode include higher rates of patient-ventilator dyssynchrony and theoretical inferiority of alveolar recruitment compared with pressure control. Ventilator dyssynchrony also can cause high variance in tidal volumes, plateau pressures, desaturations, and overall patient agitation.

Alternate modes of ventilation for difficult-to-oxygenate patients also have become more commonly used during the pandemic. Airway pressure-release ventilation (APRV) is a continuous bilevel pressure mode in which high pressures are held for a longer length of time, with quick releases to

low pressure with the intention to maximize alveolar recruitment (**Figure 2**). Although some studies evaluating APRV in patients with ARDS consider this mode a suitable alterative to standard lung-protective ventilation, the data are quite variable and few studies compare APRV directly to low tidal volume ventilation.[13] APRV also requires its own knowledge and skill set. For this reason, clinicians who are less familiar with APRV may be less inclined to use this setting. Ultimately, APRV generally is used as a mode for patients with hypoxemia refractory to standard low tidal volume ventilation.

High-frequency oscillatory ventilation (HFOV) uses an oscillator pump to deliver very high respiratory rates with tidal volumes lower than anatomical dead space to provide a constant mean airway pressure. **Figure 3** demonstrates the waveform of HFOV compared with conventional ventilation. However, summary of the evidence in HFOV for ARDS recommends against routine use of this mode of ventilation because of lack of reduction and possible increase in hospital mortality.[14] Anecdotally, HFOV has been used during the COVID-19 pandemic as a last-ditch, salvage method of ventilation for patients with refractory hypoxemia.

Sedation and analgesia are essential for patients on mechanical ventilation, to maintain ventilator compliance and reduce oxygen consumption. Some patients also may need neuromuscular blockade to induce paralysis and improve oxygenation.[15] However, sedation, analgesia, and neuromuscular blockade should be used with caution.

Additional supportive measures such as the use of corticosteroids generally is reserved for patients with moderate to severe ARDS who are early in the disease course and need oxygen support.[16] Dexamethasone is reserved for patients with ARDS who require oxygen supplementation because no clinical benefit has been found in patients who were not on respiratory support.[17] The main complication of corticosteroid use in patients with ARDS is hyperglycemia, which combined with hyperglycemia of critical illness commonly seen in patients in the ICU may be profound.

Fluid management is of high importance in the management of ARDS due to the propensity for patients to develop pulmonary edema. Conservative fluid management with diuretics and restricted fluid intake has been shown to reduce number of patient days on the ventilator and in the ICU.[18] Controversy continues about the possible detrimental effects of conservative fluid management on end-organ failure in patients with ARDS, particularly its toll on kidney function. However, current evidence demonstrates that conservative fluid management does not increase the rate of acute kidney injury and does not increase mortality when serum creatinine is adjusted for fluid status.[19]

For patients who still fail to oxygenate or ventilate on traditional supportive measures for ARDS, maximum lung support can be achieved with extracorporeal membrane oxygenation (ECMO). Venous-venous ECMO is used to bypass the lungs and is reserved for patients with severe, refractory ARDS who have not responded to standard supportive therapies. Current evidence indicates that early use of ECMO for patients with severe ARDS decreases 90-day mortality compared with conventional ventilatory support.[20] The only absolute contraindication to ECMO support is preexisting conditions that are incompatible with meaningful recovery, such as anoxia or other types or irreversible organ failure, that limit survival. Potential major complications include bleeding and thromboembolism. ECMO is resource-intensive and not available in all hospitals. Ultimately, the decision to cannulate a patient for ECMO is up to the clinician, with careful consideration of the patient's condition and possible outcomes.

PREVENTION

As research in ARDS management advances, the focus now includes prevention and early treatment. The PETAL Network (Prevention and Early Detection of Acute Lung Injury) was created in 2016 by the National Heart, Lung, and Blood Institute. This network contributes to the development of evidence-based knowledge of ARDS prevention and early treatment by creating and conducting randomized controlled studies. Active studies are evaluating the early use of neuromuscular blockading agents and the use of vitamin D on patient outcomes. In 2020, the PETAL

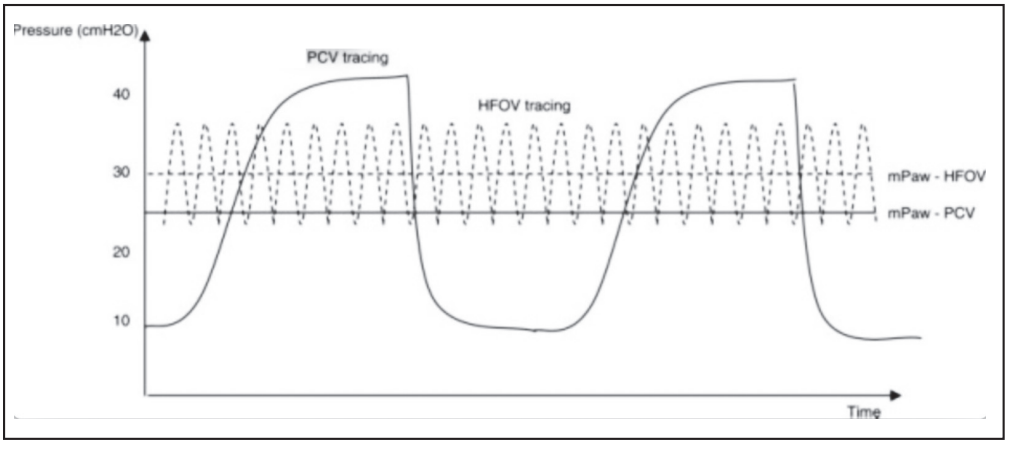

FIGURE 3. HFOV waveform compared with conventional ventilation waveform
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Network has transitioned its efforts entirely to COVID-19 research, evaluating hydroxychloroquine and collecting comprehensive retrospective and prospective data on hospitalized patients with COVID-19.

CONCLUSION

ARDS makes up a significant portion of ICU admissions with increasing incidence as the COVID-19 pandemic continues. Despite extensive research, mortality still remains high; therefore, prompt recognition by clinicians is vital. Diagnosis of ARDS may be hidden beneath the inciting event, precipitating its cause and can present similarly to a multitude of other diseases, so it must always be on the differential for patients with hypoxemia. **JAAPA**

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