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Critical Care Update

ARDS From Syndrome to Disease—*Treatment Strategies*

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To treat acute respiratory distress syndrome (ARDS), it is important to define the underlying anatomic and physiologic properties of the lung tissue being managed. If we are unable to do this, it seems logical to select treatments based on the likelihood of a positive or negative response, adjusting therapies empirically and being mindful that in a diverse patient cohort aggressive interventions carry hazards. Some of the treatments receiving recent attention will be discussed in this portion of my comments on ARDS.

Classifying the severity of ARDS requires more accurate determination of the extent of the underlying pathology. Careful matching of interventions to pathology is essential. Physiologic studies better characterizing the factors causing ventilator-induced lung injury, a major risk associated with ARDS management, are indicated before undertaking more extensive trials aimed at avoiding injury to the lung secondary to mechanical ventilation. When a damaging threshold of lung injury is determined, the indication for a better therapy in ARDS may follow.

Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med*. 2016;42:1865-1876.

Gattinoni L, Marini JJ, Quintel M. Time to rethink the approach to treating acute respiratory distress syndrome. *JAMA*. 2018;319:664-666.

Treatment factors potentially contributing to outcome from ARDS were identified in the recently published LUNG SAFE Study. This international trial was undertaken in 459 intensive care units (ICUs) in 50 countries on 5 continents. In addition to epidemiology, the LUNG SAFE trial was intended to examine factors associated with outcomes in patients with ARDS diagnosed in the era of the Berlin definition. A particular interest was modifiable risk factors including those related to patient management.

Data were stratified according to ARDS severity according to the Berlin definition as follows: mild (PaO_2/fraction of inspired oxygen [FiO_2] ratio = 201-300 mm Hg), moderate (PaO_2/FiO_2 ratio = 101-200 mmHg), and severe (PaO_2/FiO_2 ratio ≤100 mm Hg). ICU and hospital survival were evaluated. ARDS was further categorized if related to pulmonary risk factors such as pneumonia or aspiration or extrapulmonary insults such as sepsis, burns, or blood transfusion. Driving pressure (defined as the plateau pressure – positive end-expiratory pressure [PEEP]) was examined in patients with no evidence of spontaneous ventilation. In each ARDS severity category, the risk of ICU and hospital mortality was examined according to the ventilator tidal volume used, the PEEP level provided, the driving pressure, and the plateau pressure. Values were measured at the onset recorded for ARDS.

These investigators identified that older patient age, neoplastic disease, and severity of illness markers such as lower pH, lower PaO_2/FiO_2 ratio, and higher nonpulmonary organ failure scores were associated with worse patient outcome. Modifiable factors associated with increased hospital mortality included lower PEEP; higher peak inspiratory, plateau, and driving pressures; increased respiratory rate; and lower number of ICU beds.

Key aspects of ventilator management were associated with patient outcome. The use of higher PEEP in patients with moderate or severe ARDS was independently associated with improved hospital survival, supporting prior findings from a variety of trials. The lack of a relationship between tidal volume and outcome in this data set reflects the relatively limited range of tidal volumes used. Tidal volume in this study was concentrated in a range around 7 mL/kg. The association between peak, plateau, and driving pressures and both hospital and ICU outcome is also consistent with prior smaller trials. Another important finding was a positive association between lower respiratory rate and patient outcome. This observation is supported by experimental data and suggests that energy transferred to the lung is an important contributor to ventilator-induced lung injury. The finding that a lower ICU bed number was associated with higher hospital but not ICU mortality is of concern. It suggests that ICU organizational factors and resource constraints may affect ICU discharge decisions and patient outcome.

Writing Group for the PReVENT Investigators, Simonis FD, Serpa NA, et al. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial. *JAMA*. 2018;320:1872-1880.

Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA*. 2018;319:698-710.

Perhaps tidal volume is a surrogate for pressure as the most important therapy titrated in the management of patients receiving mechanical ventilation with or without ARDS. In a recent trial from the PReVENT (PRotective VENTilation) investigators, patients were assigned to a low tidal volume group starting at a tidal volume of 6 mL/kg predicted body weight (PBW) and receiving either volume-controlled or pressure

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support ventilation (PSV). Tidal volume was then decreased as indicated by 1 mL/kg every hour to a minimum of 4 mL/kg PBW. With PSV, the lowest level of pressure support was used to reach the target tidal volume with a minimum of 5 cm H_2O/pressure support. If tidal volume increased to more than 8 mL/kg PBW with the minimum pressure support, this was accepted. Patients were allowed larger tidal volumes if needed to address patient-ventilator asynchrony. An equal number of subjects were assigned to the intermediate tidal volume group started at a tidal volume of 10 mL/kg PBW using volume-controlled ventilation. If the plateau pressure exceeded 25 cm H_2O, tidal volume was decreased in increments of 1 mL/kg PBW per hour. With PSV, the pressure support level was adjusted to reach the target tidal volume while keeping the maximum airway pressure < 25 cm H_2O.

In this trial of adult patients in the ICU without ARDS receiving invasive ventilation (who were not expected to be extubated within 24 hours of randomization), a ventilator strategy using low tidal volume as described earlier was not more effective than a strategy using intermediate tidal volume with respect to ventilator-free days and survival at day 28. There was no difference between length of stay, mortality, or occurrence of pulmonary complications between groups. In fact, low tidal volume was associated with respiratory acidosis. The authors state that this is the largest randomized clinical trial to investigate the role of tidal volume management in patients without ARDS and measure a clinically relevant patient-centered outcome. Perhaps the most important factor, which received less emphasis in this work, is the careful control of plateau pressure. Patients receiving higher tidal volume had careful plateau pressure control and reduction in tidal volume if plateau pressure exceeded 25 cm H_2O. Similarly, if patients were on PSV, maximum airway pressure was controlled at 25 cm H_2O. Is it possible that achieving lower tidal volume improved outcome by associated reduction in airway pressure and pressure rather volume is most important? Finally, these authors were careful to avoid elevated respiratory rates, an outcome that could also be damaging.

Relatively few pharmacologic agents have shown promise in the management of ARDS. One trial suggested a mortality benefit in ARDS patients with a severe insult reflected in a Pao_2/Fio_2 ratio < 150 mm Hg with the use of 48 hours of cisatracurium with deep sedation. Although the exact mechanism by which neuromuscular blockade is beneficial in patients with ARDS is unclear, these medications limit the occurrence of potentially injurious phenomena such as abnormal ventilator triggering and other dyssynchrony between the patient and the ventilator. Dyssynchrony of the patient with the ventilator may lead to breath stacking in which patients get a second breath from the machine before the patient has been able to exhale the first breath. Another mechanism by which neuromuscular blockade may exert benefit is by preventing excessive spontaneous breathing early in the course of patients having moderate or severe ARDS. The amount of spontaneous breathing to allow in patients with ARDS remains unclear. Ultimately, the benefit suggested for neuromuscular blockade is avoidance of self-inflicted lung injury by the patient and risks as associated with the use of large amounts of sedation to optimize interaction of the patient and ventilator.

Scholten EL, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS with prone positioning. *Chest*. 2017;151:215-224.

An intervention that gained positive traction in the 1960s when ARDS was first described is prone positioning. Early investigators noted reduced pulmonary compliance and increased atelectasis seen with ARDS and suggested applying PEEP to improve oxygenation. To further reduce atelectasis in injured lungs, prone positioning was proposed because this maneuver would reduce pleural pressure gradients described later and restore aeration to dorsal lung segments. Subsequent studies reported that prone positioning improves oxygenation in 70% to 80% of patients with ARDS and increased the PaO_2/FiO_2 ratio by 35 mm Hg. Prone positioning has since been established as a rescue therapy in patients with severe hypoxemia. When supine, the weight of the ventral lungs, heart, and abdominal contents in the patient increase dorsal pleural pressure. This compression reduces the gradient between airway opening pressure and pleural pressure in the dorsal lung regions. An increased mass of an edematous ARDS lung further increases dorsal pressure and reduces ventilation of dependent lung regions. In addition to the weight of the heart, intra-abdominal pressure is preferentially transmitted through the diaphragm, again compressing dorsal lung regions. Although these factors tend to collapse dependent dorsal lung regions, gravitational effects on vascular pressures preferentially perfuse these regions, yielding a region of low ventilation and high perfusion reflected in hypoxemia.

Placing the patient in the prone position reduces the pressure gradient from nondependent to dependent regions, in part through gravitational effects and shape matching of the lung to the chest cavity. As a result, lung aeration distribution is more homogeneous. When supine, both gravity and the chest wall compress dependent lung segments, causing inequalities in aeration and perfusion. In the prone position, geometry favors a more equitable distribution of ventilation. This observation is supported by multiple physiologic studies.

Prone positioning reduces ventilator-induced lung injury, ventilator days, and death. Comparing ventilation of patients in the supine and prone position, prone positioning allows better dependent aeration and increased expansion of collapsed lung regions. The prone position and high PEEP also have complementary benefits. In ARDS, increased PEEP is known to prevent alveolar collapse but may promote overdistention of previously well-ventilated alveoli. Prone positioning helps to reduce these inappropriate effects of PEEP. Adding the prone position to higher PEEP settings increases lung aeration while reducing regional hyperinflation and decreasing small airway opening and closing events during the respiratory cycle.

In addition to lung-protective effects, prone positioning favorably affects cardiac and abdominal pressures. In general, total cardiac output is unchanged when patients with ARDS are placed in the prone position. However, while prone, the right atrium moves in a ventral direction so that venous return is enhanced, allowing preload responsive patients to increase cardiac output in the prone position. In addition, right ventricular afterload typically falls in the prone position because of the relief of hypoxic pulmonary vasoconstriction and the reduced volume of collapsed pulmonary parenchyma.

Prone positioning also favorably affects chest and abdominal interactions. Obesity worsens dependent dorsal lung collapse, and prone ventilation improves oxygenation in these areas during routine surgery in obese patients and obese animal models without lung injury. However, in obese humans with ARDS, prone positioning may worsen intra-abdominal hypertension and lead to renal and hepatic injury. Thus, intra-abdominal pressure should be monitored with the obese patient in the prone position. The physiology summarized previously reflects the continued support of prone positioning as an important salvage therapy in the patient with ARDS.

Patel BK, Wolfe KS, MacKenzie EL, et al. One-year outcomes in patients with acute respiratory distress syndrome enrolled in a randomized clinical trial of helmet versus facemask noninvasive ventilation. *Crit Care Med*. 2018;46:1078-1084.

Although the vast majority of studies in patients with ARDS describe optimal settings of invasive mechanical ventilation through an endotracheal tube, a smaller amount of data

can be found to support best practices with noninvasive ventilation. A rationale for this work begins with the prolonged recovery phase associated with ARDS marked by neuromuscular weakness, functional impairment, and increased resource use associated with ventilation through an endotracheal tube. Complications that many ARDS survivors experience may be a consequence of supportive care practices including deep sedation, neuromuscular blockade, and bed rest, which contribute to persistent disability. The mere presence of an endotracheal tube is often considered to be a major barrier to therapies that could improve outcome in ARDS. Patel and coworkers examined the use of noninvasive ventilation in ARDS to alter short- and long-term outcomes. More specifically, providing noninvasive ventilation using a helmet interface can reduce intubation rates and improve mortality in patients with ARDS in comparison with traditional face mask noninvasive ventilation.

In the long-term follow-up of patients managed with helmet noninvasive ventilation as part of therapy for ARDS, patients in the helmet group were more likely to be discharged home functionally independent and remain independent at 1 year after ICU admission in comparison with patients treated with face mask noninvasive ventilation during care for ARDS. The helmet group also had improved 1-year survival and less health care use. Functional limitations and poor quality of life, after hospitalization for ARDS, may reflect supportive care practices required for management with invasive mechanical ventilation including bed rest, neuromuscular blockade, and deep sedation. Helmet noninvasive ventilation may eliminate the need for an endotracheal tube in selected patients. Mortality and endotracheal intubation rates for less severe cases of ARDS may be significantly reduced when the interface for the delivery of noninvasive ventilation is a helmet. Patients in the group receiving helmet ventilation were mobilized more readily in the ICU, had less delirium, and generally did not require neuromuscular blockade with associated long-term weakness at the time of hospital discharge. Although intriguing and promising, these findings with helmet ventilation in ARDS must be considered preliminary, and the available data for this clinical approach are far less than those supporting specific strategies during invasive mechanical ventilation.

Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: a narrative review. *Chest*. 2018;154:185-195.

Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. *JAMA*. 2016;316:1583-1589.

Low tidal volume strategies in ARDS management are frequently associated with elevated arterial carbon dioxide levels. Historically, this has been accepted as a clinically insignificant finding leading to the descriptive term *permissive hypercapnia*. More recent data suggest that hypercapnia in the setting of lung-protective ventilation in ARDS may be deleterious. Using a higher respiratory rate to increase minute ventilation and lower $PaCO_2$ is sometimes used if adverse effects associated with hypercapnia become apparent. However, increasing the respiratory rate is not without risk (see earlier).

Hypercapnia induces physiologic changes in pulmonary and systemic circulation. In healthy subjects, hypercapnic acidosis causes a rightward shift of the oxyhemoglobin dissociation curve and lowers systemic vascular resistance. In patients who have undergone cardiopulmonary procedures, hypercapnia results in reduced myocardial contractility, which may trigger compensation by reflex tachycardia. Right ventricular function is compromised in the setting of postoperative hypercapnia because of increased right ventricular end-diastolic volume, decreased right ventricular ejection fraction, and a significant increase in right ventricular stroke work. These observations are in part caused by increased pulmonary vascular resistance because of the vasoconstrictive effects of hypercapnic acidosis on the pulmonary vascular bed and the associated rise in mean pulmonary artery pressure. To what degree hypercapnia and respiratory acidosis increase pulmonary vascular resistance and mean pulmonary artery pressure in the patient with ARDS is unclear. Systemic effects of hypercapnia are listed in Table 1.

Right ventricular dysfunction is common and is linked to worse outcomes in the patient with ARDS. Taken to an extreme, low tidal volume lung-protective ventilation with acceptance of permissive hypercapnia in patients with moderate to severe ARDS may lead to acute cor pulmonale and right ventricular failure. This phenomenon has been documented on recent ultrasound studies of right ventricular function during ARDS.

Two recent trials examining mechanically ventilated patients call into question the safety of hypercapnic acidosis. In the first, hypercapnic acidosis in the first 24 hours of ICU admission was associated with increased hospital mortality compared with compensated hypercapnia or normal $PaCO_2$. This adverse effect of hypercapnic acidosis on right ventricular function was observed with all types of ICU admissions. A second smaller study showed that severe hypercapnia defined as $PaCO_2 > 50$ mm Hg was associated with higher ICU mortality in a population with moderate to severe ARDS. In this work, hypercapnia independent of acidosis was associated with increased mortality, and hypercapnia plus acidosis showed an additive effect favoring increased mortality.

Table 1
Systemic Effects of Hypercapnia

Pulmonary vascular
↑ Pulmonary vascular resistance
↑ Mean pulmonary artery pressure
Immunologic
↓ Inflammatory cytokines
Vascular
↓ Systemic vascular resistance
Central nervous system
↑ Cerebral vasodilation
↑ Cerebral blood flow
Cardiovascular
↓ Contractility
↑ Heart rate
↓ Right ventricular ejection fraction
↑ Right ventricular stroke
Renal
↑ Vasoconstriction

Modified from Barnes T, Zochios V, Parhar K. Re-examining permissive hypercapnia in ARDS: a narrative review. *Chest*. 2018;154:185-195.

Strategies designed to reduce alveolar dead space and the severity of hypercapnia carry risk. Lung recruitment to facilitate ventilation in ARDS often requires finding optimal PEEP levels, but care must be taken to avoid alveolar overdistension, which can negatively affect pulmonary hemodynamics and right ventricular function. Simply using higher respiratory rates to correct hypercapnia is often not tolerated in patients with ARDS because of the development of auto-PEEP with breath stacking, another cause of significant right ventricular dysfunction.

On the other hand, prone positioning has been shown to lower the $PaCO_2$ and unload the right ventricle in select groups of patients in the critical care unit. Although limited prospective data exist supporting this assertion, prone positioning remains a valuable tool that may unload the right ventricle and improve outcomes in severe ARDS. A more invasive strategy using extracorporeal techniques to remove carbon dioxide remains controversial and awaits prospective studies. At present, a reasonable clinical goal for maintaining arterial $PaCO_2$ in ARDS is 50 mm Hg or less consistent with available evidence.

Another form of inhaled gas toxicity that has received less attention in the management of ARDS is injury secondary to excessive oxygen administration. The optimal target for oxygenation in patients with ARDS remains unclear, supported by only low-quality evidence and expert opinion. A single recent study suggests a mortality benefit for patients randomized to conservative oxygen therapy (PaO_2 of 70-100 mm Hg or pulse oximeter saturation of 94%-98%) compared with conventional therapy (PaO_2 up

to 150 mm Hg or oximeter saturation of 97%-100%). Clearly, more data are needed to better address this question.

Summary Points

- A confounding factor in research into acute respiratory distress syndrome (ARDS) is uncertainty regarding pathogenic mechanisms and triggers for this phenomenon. Thus, lacking a clear biologic definition, ARDS is better described as a syndrome without a consistent pathogenesis limiting exploration of treatment and prevention strategies.
- Recent studies are bringing aspects of clinical management of ARDS into better focus. For example, the use of higher positive end-expiratory pressure in patients with moderate or severe ARDS appears to be associated with improved outcome. Similarly, avoidance of a high respiratory rate appears beneficial.
- A recent study examining tidal volume and pressure suggests that we may be more liberal with tidal volume administration as long as dangerous airway pressure levels are not identified. This work was careful to control for excessive respiratory rates.
- Prone ventilation has long been supported for optimization of cardiopulmonary function in ARDS. This strategy, often underused, continues to receive strong support in the literature.
- Noninvasive ventilation using a helmet may be another underappreciated strategy to support the patient with less severe ARDS to avoid complications associated with endotracheal tube use, which include secretion aspiration and increased requirements for sedation, analgesia, and neuromuscular blockade.
- A growing body of literature suggests that accepting hypercapnia may be deleterious in the ARDS patient group, whereas a smaller body of data suggests limiting oxygen exposure in ARDS patients.

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