

# Updates in acute respiratory distress syndrome

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## New definition

A consensus panel led by V. Marco Ranieri, Gordon Rubenfeld, Arthur Slutsky *et al.* announced a new definition and severity classification system for acute respiratory distress syndrome (ARDS) that aims to simplify the diagnosis and better prognosticate outcomes from the life-threatening pulmonary illness.

The proposed 'Berlin definition' predicted mortality ever-so-slightly better than the existing definition (created at the 1994 American-European Consensus Conference/AECC) when applied to a cohort of 4400 patients from past randomized trials. The Berlin definition would include the following:

- (1) 'Acute lung injury' no longer exists. Under the Berlin definition, patients with  $\text{PaO}_2/\text{FiO}_2$ , 200–300 would now have 'mild ARDS.'
- (2) The onset of ARDS (diagnosis) must be acute, defined as within 7 days of some defined event, which may be sepsis, pneumonia, or simply a patient's recognition of worsening respiratory symptoms (Most cases of ARDS occur within 72 h of recognition of the presumed trigger.)
- (3) Bilateral opacities consistent with pulmonary edema must be present but may be detected on computed tomography or chest radiography.
- (4) There is no need to exclude heart failure in the new ARDS definition; patients with high pulmonary capillary wedge pressures or known congestive heart failure with left atrial hypertension can still have ARDS. The new criterion is that respiratory failure is simply 'not fully explained by cardiac failure or fluid overload,' in the physician's best estimation using the available information. An 'objective assessment'— meaning an echocardiogram in most cases – should be performed if there is no clear risk factor present such as trauma or sepsis.

The new Berlin definition for ARDS would also categorize ARDS as being mild, moderate, or severe (Table 1).

There is no change in the underlying conceptual understanding of ARDS as an 'acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue (with) hypoxemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space, and decreased lung compliance.'

Although the authors emphasize the increased power of the new Berlin definition to predict mortality compared with the AECC definition, in truth it is still poor, with an area under the curve of only 0.577, compared with 0.536 for the old definition.

Clinical variables that are widely believed to be important and useful in the management of ARDS – static compliance of the respiratory system, radiographic severity, positive end-expiratory pressure (PEEP) more than 10, and corrected expired volume more than 10 l/min – were not predictive of mortality or other clinical outcomes. After including these variables in the initial draft definition and testing them empirically in the cohort, they were all dropped from the final Berlin definition for ARDS.

The authors found a post-hoc 'high-risk profile' of patients with a 52% mortality from ARDS. These patients had severe ARDS ( $\text{PaO}_2/\text{FiO}_2$  ratio <100) and either a static compliance of less than or equal to 20 ml/cmH<sub>2</sub>O or a corrected expired volume of more than or equal to 13 l/min.

What was wrong with the old definition of ARDS:

- (a) Acute onset of hypoxemia with  $\text{PaO}_2/\text{FiO}_2$  ratio of less than or equal to 200 mmHg,

**Table 1 Grades of ARDS severity**

ARDS severity	$\text{PaO}_2/\text{FiO}_2$ *	Mortality** (%)
Mild	200–300	27
Moderate	100–200	32
Severe	<100	45

\*on PEEP 5+; \*\*observed in cohort; ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

- (b) Bilateral infiltrates on chest radiography, and
- (c) No evidence of left atrial hypertension?
- (1) No explicit criteria for defining 'acute' – leading to ambiguity regarding cases of acute-on-chronic hypoxemia.
- (2) High interobserver variability in interpreting chest radiographs.
- (3) Difficulties identifying/ruling out cardiogenic or hydrostatic pulmonary edema, especially in an era of plummeting pulmonary artery catheter use.
- (4) The PaO<sub>2</sub>/FiO<sub>2</sub> ratio is sensitive to changes in ventilator settings.

The panel's findings, endorsed by the European Society of Intensive Care Medicine, the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM), emerged from meetings in Berlin to try to address the limitations of the earlier AECC definition. The authors published their results in the 21 May 2012, online edition of *Journal of the American Medical Association*.

### **Mechanical ventilation in acute respiratory distress syndrome: an updated review**

People with ARDS are by definition severely hypoxemic, and nearly all of them require invasive mechanical ventilation. Yet mechanical ventilation itself can further injure damaged lungs (so-called ventilator-induced lung injury); minimizing any additional damage while maintaining adequate gas exchange (compatible with life) is the central goal of mechanical ventilation in ARDS and acute lung injury (ALI), its less severe form.

### **Benefits of low-tidal-volume ventilation in acute respiratory distress syndrome**

Low-tidal-volume ventilation (LTVV) reduces the damaging excessive stretch of lung tissue and alveoli (so-called volutrauma) and is the standard of care for people with ARDS requiring mechanical ventilation. Although ARMA, the largest clinical trial supporting this paradigm, was criticized both for its design and for its ethical concerns, its results (published in 2000 by ARDSNet), followed by two flawed but concordant meta-analyses [1,2] including 10 randomized trials in total, have convinced most intensivists that using low tidal volumes improves survival in people with ARDS. Taken together, the trials suggest that a strategy of LTVV (6–8 ml/kg ideal body weight) reduces the absolute mortality by about 7–9%, as compared with using 10 ml/kg or more tidal volumes (~42% mortality in control groups vs. ~34% in LTVV groups). This translates to a 'number needed to treat' of between 11 and 15 people with ARDS to prevent one death using LTVV.

### **How to use low-tidal-volume ventilation in acute respiratory distress syndrome**

The protocol from the ARMA trial can serve as a guide to performing LTVV for mechanically ventilated patients with ARDS:

- (1) Start in any ventilator mode with initial tidal volumes of 8 ml/kg predicted body weight in kg, calculated as follows:  $[2.3 \times (\text{height in inches} - 60) + 45.5 \text{ for women or } +50 \text{ for men}]$ .
- (2) Set the respiratory rate up to 35 breaths/min to deliver the expected minute ventilation requirement (generally, 7–9 l/min)
- (3) Set the PEEP to at least 5 cmH<sub>2</sub>O (but much higher is probably better) and FiO<sub>2</sub> to maintain an arterial oxygen saturation of 88–95% (PaO<sub>2</sub> 55–80 mmHg). Titrate FiO<sub>2</sub> to below 70% when feasible (although ARDSNet does not specify this).
- (4) Over a period of less than 4 h, reduce tidal volumes to 7 ml/kg, and then to 6 ml/kg.

Ventilator adjustments are then made with the primary goal of maintaining a plateau pressure (measured during an inspiratory hold of 0.5 s) less than 30 cmH<sub>2</sub>O, and preferably as low as possible, while keeping blood gas parameters 'compatible with life.' High plateau pressures vastly elevate the risk for harmful alveolar distension (also known as ventilator-associated lung injury, volutrauma). If plateau pressures remain elevated after following the above protocol, further strategies should be tried:

- (1) Further reduce tidal volume, to as low as 4 ml/kg by 1 ml/kg stepwise increments.
- (2) Sedate the patient (heavily, if necessary) to minimize ventilator-patient dyssynchrony.
- (3) Consider other mechanisms for the increased plateau pressure besides the stiff, noncompliant lungs of ARDS.

As a last resort, neuromuscular blockade can be used to reduce the plateau pressure by eliminating patient effort, muscle tone, and dyssynchrony. However, this approach has unquantified risks of long-term neuromuscular weakness and disability.

### **Permissive hypercapnia in acute respiratory distress syndrome**

This single-minded focus on reducing plateau pressures derives from the likely survival benefit from LTVV and low plateau pressures observed in clinical trials (or the harmful effects seen from using 'normal' or physiologic tidal volumes with resulting high plateau pressures in those trials).

Achieving these low plateau pressures usually requires tidal volumes low enough to result in hypoventilation, with resulting elevations in  $p\text{CO}_2$  and respiratory acidemia that can be severe, and to the treating physician, anxiety-provoking. This approach, 'permissive hypercapnia,' represents a paradigm shift from previous eras, in which achieving normal blood gas values was the main goal of mechanical ventilation.

How 'permissive' can one be?. Mechanically ventilated patients with ARDS appear to tolerate very low blood pH and very high  $p\text{CO}_2$ s without any adverse sequelae (defying physicians' anxieties based on intuition, training, and medical lore):

- (1) The current consensus suggests that it is safe to allow the pH to decrease to at least 7.20.
- (2) The actual  $p\text{CO}_2$  is of little importance.
- (3) When the pH decreases below 7.20, many physicians choose to administer sodium bicarbonate, carbicarb, or tris-hydroxymethyl aminomethane to maintain a blood pH between 7.15 and 7.20.
- (4) However, it is unknown whether such correction of acidemia is helpful, harmful, or neither (good evidence is lacking for any of these hypotheses).

Conditions in which permissive hypercapnia for ARDS could theoretically be harmful include cerebral edema, mass lesions, or seizures, active coronary artery disease, arrhythmias, hypovolemia, gastrointestinal bleeding, and possibly others. These are hypothetical harms based on the pathophysiology and not on the outcome data, whereas the harm of ventilator-induced lung injury and the benefits of a protective ventilator strategy in ARDS are real and known. The potential risks of hypercapnia in such patients must be weighed against the risks of ARDS, and the therapy must be individualized.

### **Limitations associated with the use of a plateau pressure for acute respiratory distress syndrome**

Patients with reduced chest wall compliance – most commonly due to obesity – may have higher plateau pressures at baseline and during ARDS than nonobese patients. It is possible that in some obese patients, titrating tidal volumes to plateau pressures less than 30  $\text{cmH}_2\text{O}$  may be inadequate and result in worsened hypoventilation. There are no recommendations to treat obese patients with ALI/ARDS differently from nonobese patients with regard to mechanical ventilation. Esophageal manometry is considered superior to plateau pressures through its measurement of transpulmonary pressure, considered as a more

precise measure of potentially injurious pressures in the lung. Because it is invasive and the probes are prone to migration, esophageal manometry is not used widely.

### **Prone positioning in acute respiratory distress syndrome**

Prone positioning (face-down) improves gas exchange and has long been used as an adjunctive or salvage therapy for severe or refractory ARDS. Prone positioning is gaining credibility as a new standard of care for ARDS after a multicenter trial published in 2013 demonstrated a drastic near 50% relative risk reduction and a 17% absolute risk reduction for mortality. Patients were kept in the prone position for 16 h a day in that trial, which was conducted at 27 European centers highly experienced with prone positioning for ARDS. The benefits of prone positioning have not yet been replicated in a large US trial, but a meta-analysis of six randomized trials also concluded that prone positioning saves lives in ARDS when added to a lung-protective ventilatory strategy.

### **High PEEP versus low PEEP in acute respiratory distress syndrome**

A strategy using higher PEEP along with LTVV should be considered for patients receiving mechanical ventilation for ARDS. This suggestion is based on a 2010 meta-analysis of three randomized trials ( $n = 2229$ ) testing higher against lower PEEP in patients with ALI or ARDS, in which ARDS patients receiving higher PEEP had a strong trend toward improved survival.

However, patients with milder ALI ( $\text{PaO}_2/\text{FiO}_2$  ratio  $>200$ ) receiving higher PEEP had a strong trend toward harm in that same meta-analysis. Higher PEEP can conceivably cause ventilator-induced lung injury by increasing plateau pressures, or cause pneumothorax or decreased cardiac output. These adverse effects were not noted in the largest ARDSNet trial (2004) testing high PEEP versus low PEEP.

### **Predicting survival and outcomes after acute respiratory distress syndrome**

In a 2012 retrospective analysis in *Journal of the American Medical Association* including data from over 4400 patients with ARDS enrolled in randomized trials, only the severity of hypoxemia (low  $\text{PaO}_2/\text{FiO}_2$  ratio) was predictive of mortality. Commonly used clinical parameters of severity (static compliance, the degree of PEEP, and the extent of opacities on chest radiography) were not predictive of the outcome. A 'high-risk' patient profile with a 52% mortality was

identified *post hoc*, comprised of severe ARDS ( $\text{PaO}_2/\text{FiO}_2$  ratio  $<100$ ) with either a high corrected expired volume of 13 l/min or more or a low static compliance less than 20 ml/cmH<sub>2</sub>O. Reviews of ARDS outcomes suggest that most people who survive ARDS recover pulmonary function, but may remain impaired for months or years in other domains, both physically and psychologically.

### **Alternative/rescue ventilator modes and extracorporeal membrane oxygenation in acute respiratory distress syndrome**

Some patients with severe ARDS develop severe hypoxemia or hypercarbia with acidemia despite optimal treatment with low-tidal-volume mechanical ventilation. In these situations, alternative, salvage or 'rescue' ventilator strategies are often used. Their common goal is to maintain high airway pressures to maximize alveolar recruitment and oxygenation, whereas minimizing alveolar stretch or shear stress. The most commonly used alternative ventilatory strategies are high-frequency oscillatory ventilation (HFOV) or airway pressure release ventilation (or 'bilevel'). HFOV is not appropriate as a first-line treatment for ARDS. More information on HFOV and airway pressure release ventilation is provided here.

### **Extracorporeal membrane oxygenation**

Extracorporeal membrane oxygenation has also become a more commonly used salvage therapy for ARDS, thanks to improvements in technology making it safer and more feasible to administer. Its use is limited to specialized centers, and there are no randomized trials (since CESAR) defining its benefits or guidelines for its wider use.

### **Recent research findings/controversies in acute respiratory distress syndrome**

$\beta$ -Agonist infusions were found to be harmful to ARDS patients in the 2011 BALTI trials. Trophic (minimal) tube feeds appeared equivalent to full-calorie tube feeds for ALI/ARDS patients in the 2011 EDEN trial. About 48 h of neuromuscular blockade early in the course of severe ARDS appeared to improve mortality in a 2010 randomized trial. These findings are mentioned for informational purposes only, without any recommendation as to their use.

### **Oxygenation in acute respiratory distress syndrome**

The assumption that elevating the arterial oxygenation improves outcomes in patients with hypoxemia

secondary to ARDS underpins many studies in this field. However, data from clinical trials in patients with ARDS challenge this assumption, and frequently, oxygenation and long-term outcome seem to be unrelated. Although some studies have reported a relationship between arterial oxygenation and mortality, a systematic review of 101 clinical studies of ARDS concluded that the  $\text{PaO}_2/\text{FiO}_2$  ratio was not a reliable predictor of the outcome. A variety of interventions including HFOV, prone positioning, inhaled nitric oxide, and extracorporeal membrane oxygenation have been shown to improve arterial oxygenation in patients with ARDS without yielding an outcome benefit. Furthermore, different strategies of mechanical ventilation have led to (a) improved oxygenation but an unchanged outcome, (b) improved outcome but unchanged oxygenation, and (c) deterioration in oxygenation but an unchanged outcome. Taken together, these data do not support the assumption that improved oxygenation has a causative relationship with improved clinical outcomes in patients with ARDS.

Three important considerations relate to this discussion. First, supplemental oxygen is a supportive intervention serving to correct a consequence of the underlying pathophysiology, rather than to treat a cause or reverse a disease process. Second, cellular hypoxia is not a prominent feature of ARDS. Third, death in these studies is rarely due to intractable hypoxemia or respiratory failure, but commonly from the underlying cause of ARDS (e.g. systemic inflammation due to sepsis). Taken together, these data suggest that the underlying assumption merits testing through adequately powered well-designed clinical trials.

### **Permissive hypoxemia**

The concept of target-defined arterial oxygenation described precise control of arterial oxygenation, and is echoed in a recently published guideline for acutely ill patients that suggests normal or near normal oxygenation as the goal for oxygen therapy rather than unrestricted administration of oxygen to hypoxemic patients. However, whereas targeting normoxemia may be the best practice in acute situations, it may be neither achievable nor beneficial in critically ill patients exposed to subacute or sustained hypoxemia. In patients who have had sufficient time to be adapting or adapted to a subacute or sustained hypoxemia, a strategy of permissive hypoxemia may improve outcomes because of the marginal benefit (and the potential increased harm) that arises from increasing the arterial oxygenation to normal. In other words, the goal of permissive hypoxemia is to reduce morbidity and mortality in selected hypoxemic patients who have

had sufficient time to adapt to this state, by targeting lower levels of arterial oxygenation than are currently acceptable.

## Acknowledgements

### Conflicts of interest

None declared.

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