

# Acute Respiratory Distress Syndrome

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The acute respiratory distress syndrome (ARDS) and the related acute lung injury (ALI) syndromes are forms of Type I or acute hypoxemic respiratory failure (AHRF). This form of lung dysfunction rises from diseases causing collapse and/or filling of alveoli with the result that a substantial fraction of mixed venous blood traverses nonventilated airspaces, effecting a right-to-left intrapulmonary shunt (Figure 1, panel b). In addition to the adverse consequences upon gas exchange, interstitial and alveolar fluid accumulation result in an increase in lung stiffness, imposing a mechanical load with a resulting increase in the work of breathing (Figure 1, panel a). Uncorrected, the gas exchange and lung mechanical abnormalities may eventuate in tissue hypoxia, respiratory arrest, and death (see Figure 2). When this form of respiratory failure arises from acute lung injury with diffuse alveolar damage and flooding, it is termed ARDS.

## Classification and Definition

To a first approximation, the disorders causing AHRF may be divided into diffuse lesions such as pulmonary edema, and focal lung lesions such as lobar pneumonia (Table 1). Since the distribution

of airspace involvement may have implications for the response to interventions such as positive end-expiratory pressure (PEEP), this nosology is of both therapeutic and didactic value.

Low-pressure pulmonary edema, termed ARDS as a clinical entity, results from injury to the lung microcirculation sustained from direct lung insults (*eg*, aspiration, inhalation, or infectious agents) or indirectly by systemic processes (*eg*, sepsis, traumatic shock with large volume blood product resuscitation). The former is termed “pulmonary” ARDS and the latter “extrapulmonary” ARDS. Some studies have suggested different lung mechanical properties between these entities and a different response to ventilator maneuvers directed at alveolar recruitment.

In addition to the distinction between pulmonary and extrapulmonary forms of ARDS/ALI, it is also useful to distinguish between the early phases of acute lung injury and events occurring subsequently (Figure 3).

By light microscopy, early ARDS/ALI is characterized by flooding of the lung with proteinaceous fluid and minimal evidence of cellular injury. By electron microscopy, changes of endothelial cell swelling, widening of intercellular junctions, increased numbers of pinocytotic vesicles, and disruption and

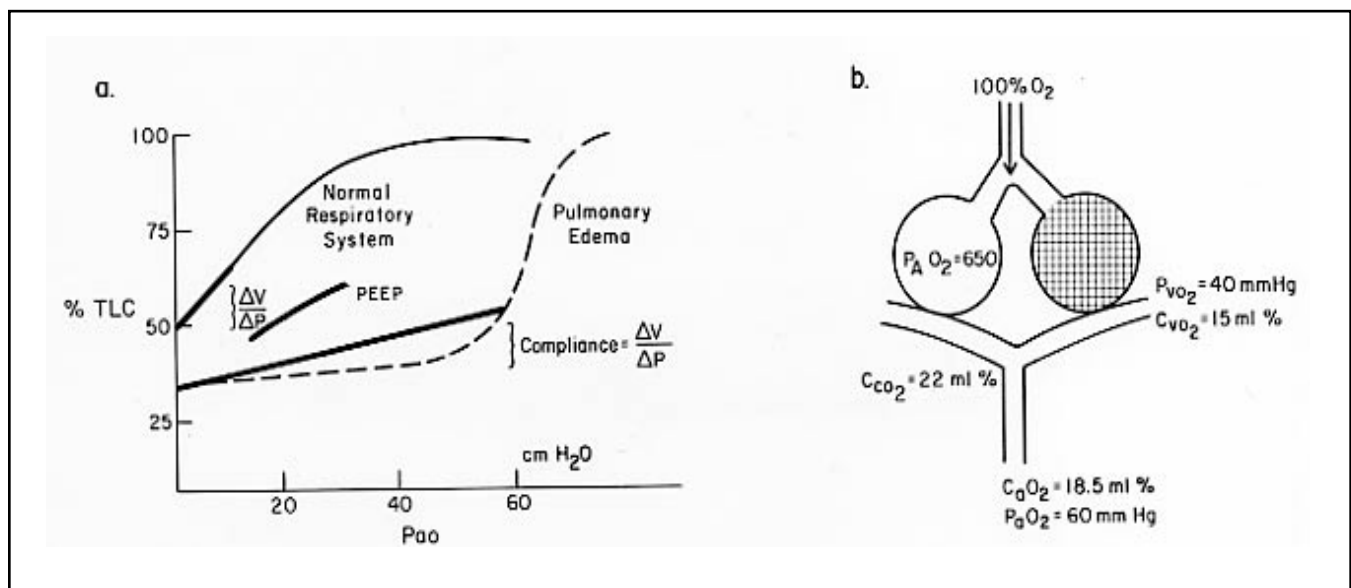
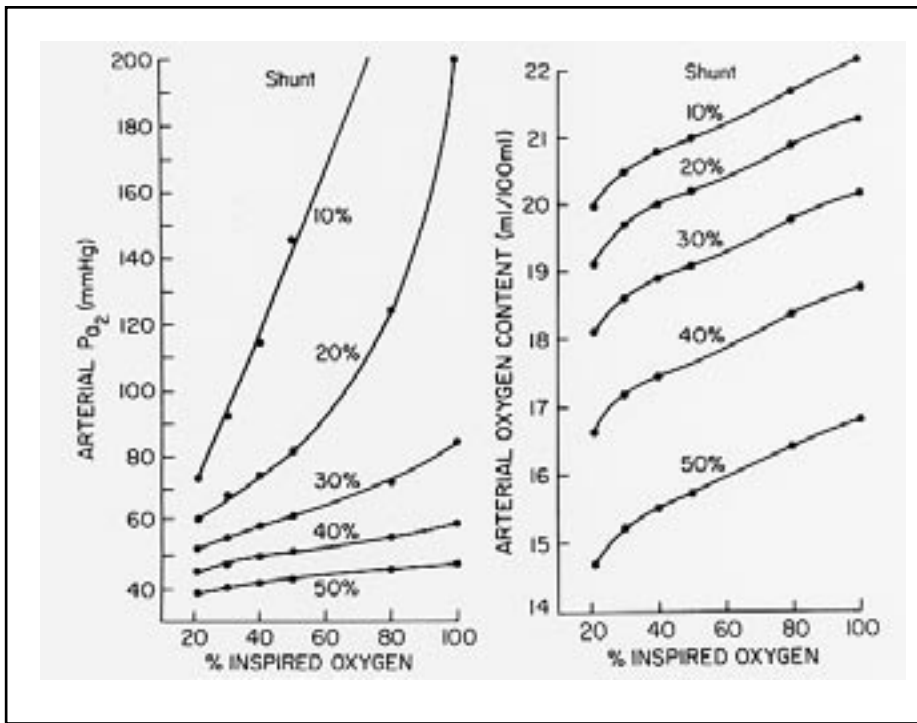
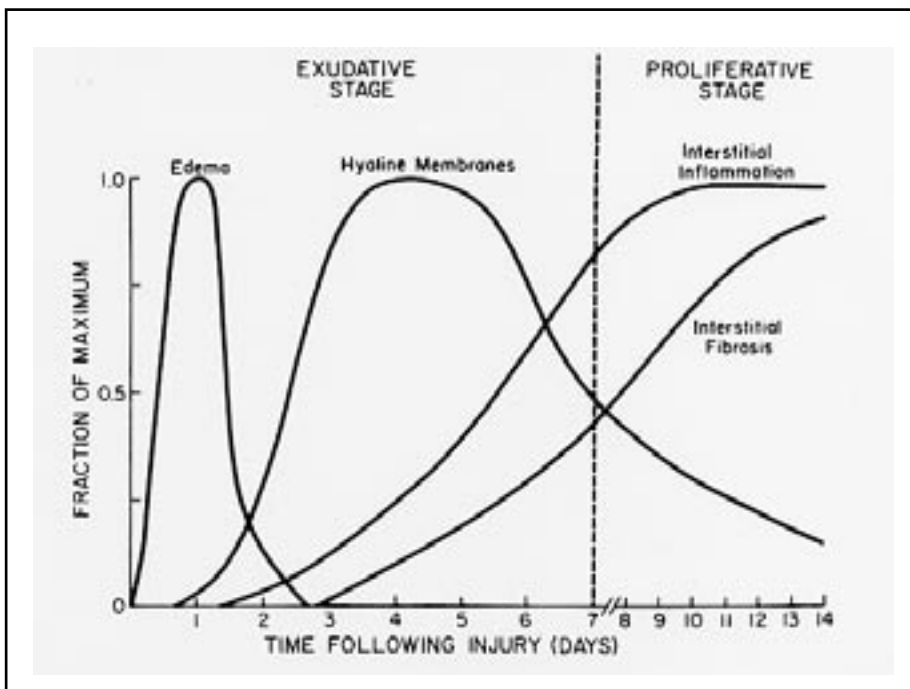


Figure 1.



**Figure 2.** Left panel: The impact of shunt fraction on oxygenation—note that when shunt is 30% and above, the response to oxygen as judged by arterial  $P_{O_2}$  is minimal. Right panel: Even though the arterial  $P_{O_2}$  changes with oxygen are minimized by large shunt fraction, the increase in arterial oxygen content are large given the steep slope of the hemoglobin-oxygen dissociation curve in this range.



**Figure 3.** Depiction of the pathologic phases of acute lung injury/acute respiratory distress syndrome.

**Table 1.** Causes of Acute Hypoxic Respiratory Failure

Homogenous Lung Lesions (producing pulmonary edema)	
Cardiogenic or Hydrostatic Edema	
Left ventricular (LV) failure	
Acute LV ischemia	
Accelerated or malignant hypertension	
Mitral regurgitation	
Mitral stenosis	
Ball-valve thrombus	
Volume overload, particularly with co-existing renal and cardiac disease	
Permeability or Low-Pressure Edema (ARDS)	
Most Common	
Sepsis and sepsis syndrome	
Acid aspiration	
Multiple transfusions for hypovolemic shock	
Less Common	
Near drowning	
Pancreatitis	
Air or fat emboli	
Cardiopulmonary bypass	
Pneumonia	
Drug reaction or overdose	
Leukoagglutination	
Inhalation injury	
Infusion of biologics (eg, interleukin 2)	
Ischemia-reperfusion (eg, post-thrombectomy, post-transplant)	
Edema of Unclear or "Mixed" Etiology	
Re-expansion	
Neurogenic	
Post-ictal	
Tocolysis-associated	
Diffuse Alveolar Hemorrhage	
Microscopic angiitis	
Collagen vascular diseases	
Goodpasture's syndrome	
Severe coagulopathy and bone marrow transplant	
Retinoic-acid syndrome	
Focal Lung Lesions	
Lobar Pneumonia	
Lung Contusion	
Lobar Atelectasis (acutely)	

denudation of the basement membrane are prominent. This early phase of diffuse alveolar damage (DAD) has been termed **exudative**, and is a period of time during which pulmonary edema and its effects are most pronounced and intrapulmonary shunt is a primary problem dictating ventilatory strategies.

Over the ensuing days, hyaline membrane formation in the alveolar spaces is prominent and inflammatory cells become more numerous. The latter phase of DAD is dominated by disordered healing. This can occur as early as 7 to 10 days after initial injury and often exhibits extensive pulmonary fibrosis, not dissimilar microscopically to patients with longstanding pulmonary fibrosis. This has been termed the **proliferative** phase of DAD. Pulmonary edema may not be as prominent in this latter phase of lung injury, and the clinician managing the patient is challenged by the large dead space fraction and high minute ventilation requirements. These patients may also exhibit progressive pulmonary hypertension—even if the pulmonary circulation was normal at baseline, slightly improved intrapulmonary shunt which is less responsive to PEEP, further reduction in lung compliance, and a tendency toward creation of Zone I conditions of the lung if the patient develops hypovolemia.

Patients with ARDS/ALI have a large number of underlying medical and surgical etiologies and there has been broad recognition of a need for specific definitions of these entities. The widely applied definitions offered by a joint American-European Consensus Conference published in 1994 are given in Table 2.

Scoring systems have also been used to grade patients with ALI/ARDS. Despite the large de-

**Table 2.** The 1994 American-European Consensus Conference Definitions of Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

	Timing	Oxygenation	CXR	Ppw
ALI Criteria	Acute onset	$\text{PaO}_2/\text{FiO}_2 < 300$ mm hg (regardless of PEEP level)	Bilateral infiltrates	< 18 mm Hg or no clinical evidence right atrial hypertension
ARDS Criteria	Acute onset	$\text{PaO}_2/\text{FiO}_2 < 200$ mm hg (regardless of PEEP level)	Bilateral infiltrates	< 18 mm Hg or no clinical evidence right atrial hypertension

CXR, chest radiograph; Ppw, pulmonary capillary wedge pressure;  $\text{FiO}_2$ , fraction inspired oxygen; PEEP, positive end-expiratory pressure.

rangements in lung physiology in these patients, initial measurements of gas exchange and lung mechanics have not been very useful to predict mortality in these patients. One recent report, however, indicated that the dead space fraction measured during the first day of mechanical ventilation was a powerful determinant of survival—the odds ratio for mortality associated with each increase of dead-space fraction of .05 was 1.45 (95% CI 1.15-1.83,  $p=.002$ ) (Figure 4).

## Treatment

This discussion will focus upon ventilator and circulatory strategies for patients with ARDS/ALI, but it cannot be overemphasized that simultaneously a search for and treatment of the underlying cause of the lung failure must be conducted. Absent an identification and treatment of the underlying process(es) causing lung injury, supportive therapy alone will likely ultimately result in mounting complications and irreversible organ failures.

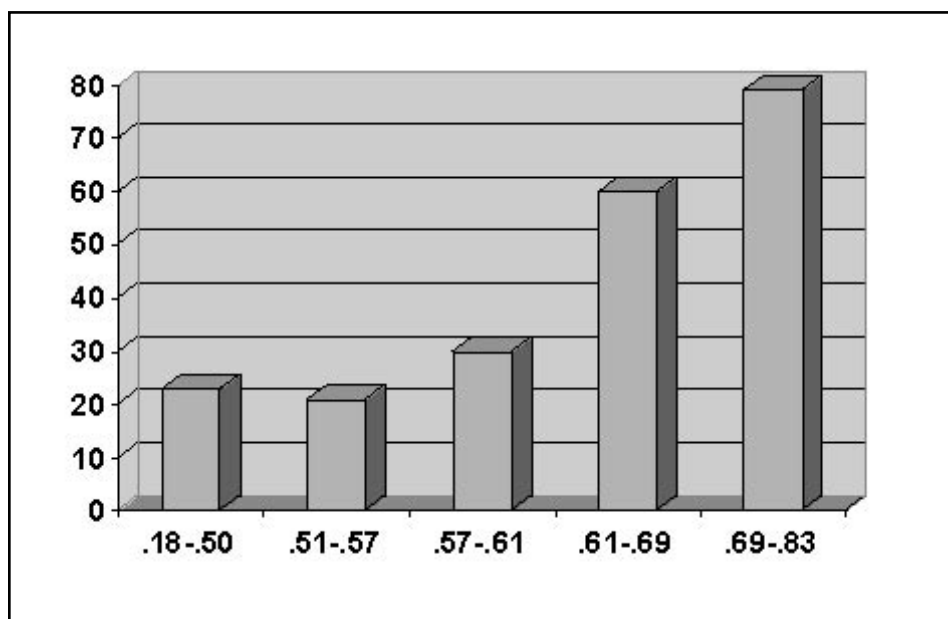
### Ventilatory Management of ARDS

#### *Lung Mechanics, Ventilator-Induced Lung Injury, and Ventilator-Associated Lung Injury*

Over the past decade or more, a body of knowledge has accrued from both bench and clinical investigations which has motivated intensiv-

ists to reconsider how they ventilate patients with ARDS. Much of this work was based upon early observations that mechanical ventilation using large tidal volumes and high inflation pressures could cause lung injury in animals with normal lungs or worsen a baseline lung injury. This phenomenon was termed ventilator-induced lung injury (VILI). VILI is indistinguishable morphologically, physiologically, and radiologically from DAD caused by other etiologies of acute lung injury. VILI is unique because one can identify that mechanical ventilation is the cause of lung injury, and hence the term *ventilator-induced lung injury*. Ventilator-associated lung injury (VALI) is defined as lung injury which resembles ARDS and which occurs in patients on mechanical ventilation. VALI is invariably associated with pre-existing lung pathology such as ARDS. However, while the experimental data is overwhelming in demonstrating the existence of VILI, one cannot be sure in any particular case whether and to what extent VALI is caused by a particular ventilator strategy, rather VALI is only *associated* with mechanical ventilation.

Studies in animal models of VILI have demonstrated that lung injury during mechanical ventilatory support appears related to the distending volume to which the lung is subjected, rather than the distending pressure as measured at the mouth. For instance, in animal experiments in which the chest is banded and mechanical ventilation is conducted with high airway pressures but low tidal volumes



**Figure 4.** The observed mortality according to the quintile of dead-space fraction in 179 patients with ARDS (from Nuckton et al; N Engl J Med, 2002; 346:1281).

resulting from the restricted chest wall, lung injury is not present. Such observations have caused the term “volutrauma” to be coined for this form of microstructural injury, a refinement of the standard term “barotraumas” applied to the grosser forms of extra-alveolar air collections that are sought on routine radiographs obtained on patients undergoing mechanical ventilation.

In addition to the detrimental effects of over-distension, numerous investigations have suggested a protective or ameliorating effect of PEEP on VILI. This protective effect has been postulated to result from the action of PEEP to avoid alveolar collapse and reopening. In the aggregate, these studies offer a view of VILI that is portrayed in Figure 5—that during the respiratory cycle, alveolar opening and collapse occur if end-expiratory pressure is zero or only modestly positive, and depending on end inspiratory lung volume, alveolar overdistension may occur.

In both animal models of lung injury and patients with ARDS, the respiratory system inflation pressure volume (PV) curve exhibits a sigmoidal shape, with a lower inflection point (LIP) and an upper inflection point (UIP). Marked hysteresis is often noted when the inflation and deflation limbs are compared. The presence of the LIP is consistent with the edematous lung behaving as a two-compartment structure, with a population of alveoli exhibiting near normal compliance and another recruitable only at higher transpulmonary

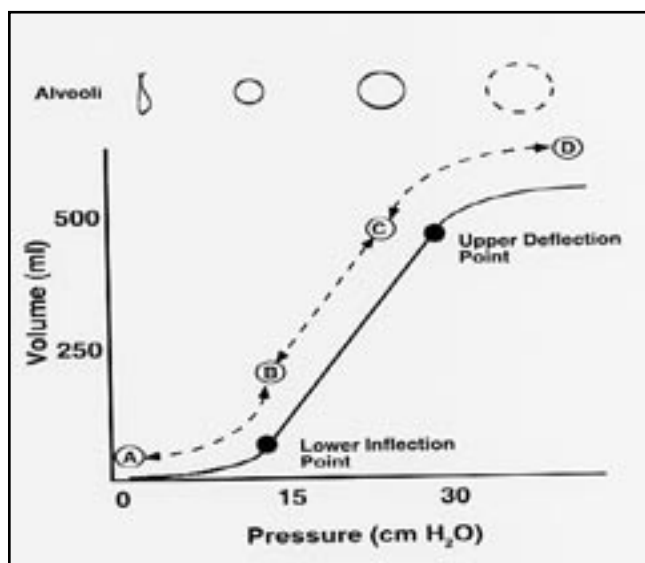
pressure. As transpulmonary pressure is raised to the LIP, effecting alveolar recruitment, lung compliance improves as reflected by the increase in the slope of the PV curve. Volume tends to increase in a nearly linear fashion as pressure is increased, until the UIP is reached, with a flattening of the curve taken to represent alveolar over-distension with the attendant risks of alveolar injury.

### *Clinical Studies of Ventilator Strategies for ARDS*

These descriptions of VILI in animals and physiologic observations in patients resulted in strategies that have been tested at the bedside and demonstrated improved patient outcome. In the field of critical care medicine, this is one of the most substantive examples of bench-to-bedside transfer of knowledge that now provides an evidence-based approach to patient care.

Hickling and colleagues reported a favorable impact on survival of tidal volume ( $V_T$ ) reduction and permissive hypercapnea in the management of patients with ARDS, comparing outcome to historical controls. These studies were limited by the lack of a randomized prospective controlled design, particularly in light of findings that the survival of patients with ARDS in the same time-frame is likely improving apart from the details of mechanical ventilatory support.

The first prospective randomized trial testing a strategy of limiting  $V_T$  and utilizing PEEP to avoid alveolar recruitment-derecruitment (so-called “open lung” ventilation) was conducted by Amato and colleagues, who randomized patients with ARDS to two treatments: (1) assist-control ventilation with tidal volumes of 12 mL/kg, PEEP sufficient to maintain an adequate  $SAO_2$  on  $FiO_2 < 0.6$ , and respiratory rates sufficient to maintain arterial carbon dioxide levels of 25 to 38 mm Hg, no efforts were made to control peak inspiratory or plateau airway pressures (“conventional” approach); or (2) pressure-controlled inverse ratio ventilation, pressure-support ventilation, or volume-assured pressure-support ventilation with tidal volumes less than 6 mL/kg, recruitment maneuver, peak pressures less than 40 cm  $H_2O$ , and PEEP titrated to maintain lung inflation above the lower inflection point (“open-lung” approach). Patients managed with the “open-lung” approach demonstrated a more rapid recovery of pulmonary compliance, decreased requirement for high  $FiO_2$ , a lower rate



**Figure 5.** An idealized and simplified depiction of the pressure volume curve of the injured lung during inflation, with the state of alveolar collapse and inflation.

of barotrauma, a higher rate of liberation from the ventilator, decreased death associated with respiratory failure, and a decreased mortality at 28 days (although not at hospital discharge).

While these results were striking, a number of concerns regarding this study deserve consideration. The number of patients included in the study was small (only 53). Furthermore, there were multiple treatment differences between the two groups, including PEEP strategy,  $V_T$ ,  $PCO_2$ , minute ventilation, lung recruitment maneuvers, and mode of ventilation. Importantly, mortality was extremely high in the conventional ventilation group (71%), and the early differences in mortality seen between the groups did not seem consistent with the two ventilator strategies differing by the accrual of progressive lung injury. Finally, patients with severe metabolic acidosis, a common feature of patients with overwhelming sepsis and ARDS, were excluded from study. Even if one accepts the results of this study, perhaps the benefit was simply due to  $V_T$  reduction, not to the PEEP strategy. Even if this PEEP strategy prevented VILI, the PEEP value selected from the LIP on inflation of edematous lungs from zero end expiratory pressure is considerably larger than the PEEP value required to maintain alveolar recruitment during tidal ventilation on PEEP. In addition, several other investigations evaluating the effect of  $V_T$  manipulation on outcome did not show a similar salutary effect of low  $V_T$  ventilation.

The controversy over proper tidal volumes for ventilation of patients with ARDS has been largely resolved by the performance of a trial conducted by the NIH-funded ARDSnet, a network of 10 centers in 24 hospitals comprising 75 intensive care units that enrolled 861 patients. Patients were randomized to a strategy of either 12 mL/kg  $V_T$  or 6 mL/kg  $V_T$ , based on ideal body weight. If plateau airway pressure ( $P_{plat}$ ), used as a surrogate of end inspiratory lung “stretch,” exceeded 30 cm  $H_2O$  pressure in the low  $V_T$  group, tidal volume was further reduced as necessary to reduce  $P_{plat}$  to this target value. The experimental protocol could be summarized as shown in Table 3.

The trial was stopped sooner than the anticipated endpoint since the findings were striking. The strategy achieved a significant difference in tidal volumes as intended—the mean tidal volumes on days 1 to 3 were 6.2 and 11.8 mL/kg in the low and high groups respectively ( $p < .001$ ), associated with  $P_{plat}$  of 25 and 33 cm  $H_2O$  respectively ( $p < .001$ ). PEEP levels were minimally higher in the low  $V_T$

group from days 1-3 (averaging less than 1 cm  $H_2O$  and lower on day 7). The low  $V_T$  group had a modest increase in  $Paco_2$  relative to the traditional group and a very modest decrease in pH; the potential for greater degrees of respiratory acidosis between the groups was minimized by the higher respiratory rates used in the low  $V_T$  group. The primary endpoint of the study, 28-day mortality, was significantly improved with low  $V_T$  ventilation, falling from 39.8% in the traditional group to 31.0% with low  $V_T$  ventilation ( $p = .007$ ). In addition, the number of ventilator-free days in the first 28 days was greater in the low  $V_T$  group.

This trial is a benchmark and confirms earlier basic and clinical studies suggesting low  $V_T$  ventilation can be protective for patients with ARDS and will improve outcome. Perhaps the best evidenced-based recommendation for routine management of patients with ARDS undergoing mechanical ventilation is to implement the ARDSnet protocol. While questions surround other elements of ventilatory strategy—the “best PEEP” level, the trade-off between  $FIO_2$  and PEEP, the use of recruitment maneuvers, patient positioning—the current evidence strongly supports the use of the ARDSnet strategy pending additional information to guide these other components of ventilatory support.

**Table 3.** ARDSnet Low Tidal Volume Protocol

Variable	Protocol
Ventilator mode	Volume assist-control
Tidal volume	$\leq 6$ mL/kg predicted body weight
Plateau airway pressure	$\leq 30$ cm $H_2O$
Vent rate/pH goal	6-35/min, adjusted to achieve arterial pH $> 7.30$ if possible
Inspiratory flow	Adjust for I:E of 1.1:1.3
Oxygenation	$55 \leq PaO_2 \leq 80$ mm Hg or $88 \leq SaO_2 \leq 95\%$
$FIO_2$ /PEEP combinations	.3/5, .4/5, .4/8, .5/8, .5/10, .6/10, .7/10, .7/12, .7/14, .8/14, .9/14, .9/16, .9/18, 1.0/18, 1.0/22, 1.0/24
Weaning	Attempt by PS when $FIO_2$ /PEEP $< .4/8$

Predicted body weight for males =  $50 + (2.3 \times (\text{height in inches} - 60))$  or  $50 + (.91 \times (\text{height in cm} - 152.4))$   
 Predicted body weight for females =  $45 + (2.3 \times (\text{height in inches} - 60))$  or  $45 + (.91 \times (\text{height in cm} - 152.4))$

Despite these very convincing data from a well-conducted trial and the peer-review of the report of this study, some have called the results into question. A recent meta-analysis by Eichacker and colleagues has suggested that the ARDSnet  $V_T$  trial may have “missed” the ideal  $V_T$  for these patients by not testing  $V_T$  in the range between 6 and 12 mL/kg, and that while survival was better for patients with lower  $V_T$ , these results point more to the detrimental effects of very high tidal volumes and not to the superiority of lower tidal volumes. While this argument is interesting in a theoretical sense, there are really no data to support this contention and most experts would agree that the ARDSnet trial indeed tested the general range of  $V_T$  used in managing these patients and that the results support the low  $V_T$  approach.

### *Practical Points for Managing the Patient with ALI/ARDS*

Upon presentation the patient should receive oxygen provided by high-flow or rebreather mask, although these devices rarely achieve a tracheal  $F_{IO_2}$  much above 0.6 in dyspneic, tachypneic patients. The administration of supplemental oxygen is a diagnostic as well as therapeutic maneuver. Patients whose oxygenation improves dramatically with supplemental oxygen generally have a small shunt and a larger component of ventilation-perfusion mismatch (or hypoventilation). Even when the  $P_{aO_2}$  improves only slightly, indicating a large shunt, oxygen delivery may rise importantly, due to the steep nature of the hemoglobin saturation relationship at low  $P_{aO_2}$  (see Figure 2). The role of noninvasive positive-pressure ventilation (NIPPV) has not been established in ARDS. Although we have used NIPPV successfully in this setting, we believe it is generally not a good choice and patients must be carefully selected. Since the course of ARDS is usually longer than patients will tolerate NIPPV, and since ARDS is so often associated with hemodynamic instability, coma, and multiorgan system failure (including ileus), we believe all but exceptional patients should be endotracheally intubated.

Intubation should be performed early and electively when it is clear that mechanical ventilation will be required, rather than waiting for frank respiratory failure. If hypoperfusion is present, as in the patient with hypotension, cardiovascular instability, or the hyperdynamic circulation of

sepsis, oxygen delivery may be compromised not only by hypoxemia but by an inadequate cardiac output as well. In this circumstance, sedation and muscle relaxation should be considered as a means to diminish the oxygen requirement of the skeletal muscles. Patients with extreme hypoxemia despite ventilator management as described below may also benefit from sedation or paralysis.

The initial ventilator settings should pursue the protocol given in Table 3. While the use of low  $V_T$  is strongly supported by current evidence, the proper PEEP level is less clear. Some intensivists recommend a “least PEEP” approach, using PEEP only as necessary to achieve adequate oxygenation and avoid toxic levels of  $F_{IO_2}$  (although these thresholds are not well established). Others would recommend higher PEEP levels with a goal of achieving maximal lung recruitment and avoiding mechanical events such as collapse-reinflation that could lead to VALI. Some even advocate use of the PV curve of the lung measured during the respiratory cycle as a guide to this PEEP titration. Data do not support one or another approach strongly, and the ARDSnet is currently completing a trial comparing low and high PEEP strategies. In the interim, use of the ARDSnet protocol seems prudent.

Regardless of specific strategy, reducing PEEP, even for short periods of time, is often associated with alveolar derecruitment and hence rapid arterial hemoglobin desaturation. Thus, once endotracheal tube suctioning has been accomplished for diagnostic purposes, nursing and respiratory therapy staff should be instructed to keep airway disconnections to a minimum, or to use an in-line suctioning system that maintains sterility and positive pressure, usually via the suctioning catheter residing in a sterile sheath and entering the endotracheal tube via a tight-sealing diaphragm. These suctioning systems are generally effective for lesser levels of PEEP (<15 cm  $H_2O$ ) but often leak if higher levels are attempted.

### *Innovative Therapies for ARDS*

While the general strategy described above will provide adequate ventilatory support for the majority of patients with ALI/ARDS, a fraction of patients will have severe hypoxemia or other adverse consequences of these approaches, and innovative or salvage therapies have been reported in the literature. In general these approaches are

not supported by large prospective trials (or trials have been conducted without benefit seen) but they may have some role in individual patient management.

*Prone Position:* Multiple studies have shown that a substantial fraction of patients with ARDS exhibit improved oxygenation with prone positioning. Some studies suggest this maneuver enhances lower lobe recruitment and thus would have the potential to not only improve gas exchange but perhaps reduced VALI and ultimate patient outcome. A recent large prospective trial evaluated proning in patients with ALI/ ARDS and did not see a benefit. In subset analysis, there did appear to be a trend to improved outcome in patients with more severe physiologic derangement. In addition, this study has been criticized for the relatively short periods of proning that were employed. Further studies of this strategy are ongoing.

*High Frequency Ventilation:* If excessive lung excursion is associated with injury to the lung, then it seems reasonable that ventilation with very small tidal volumes at high frequencies would be associated with the least possible VILI, and would be associated with improved outcome. High-frequency jet ventilation (HFV) typically employs tidal volumes of 1 to 5 mL (or higher) and respiratory rates of 60 to 300 breaths/min. Gas exchange is poorly understood under these conditions, but is thought to occur as much through augmented axial diffusion as through bulk flow. Unfortunately, multiple trials of high-frequency ventilation in adults have failed to demonstrate any benefit compared to mechanical ventilation. It is interesting to note that HFV has never been associated with either improved oxygenation, reduced barotrauma, or decreased days of mechanical ventilation. These are all outcomes that would be reasonably expected as a logical extension of the physiology and concerns driving open lung ventilation. That they have not been observed suggests that all previous investigations of HFV were conducted using the wrong guidelines for ventilation (*ie*, striving to maintain normocarbida), or that some other effect not yet understood precludes benefit from this technique. Future studies of HFV should compare this technique to ventilation using the low  $V_T$  ventilation as described in the ARDSnet trial and will have to demonstrate benefit compared to these strategies to gain acceptance.

*Extracorporeal Gas Exchange:* The use of extracorporeal gas exchange (ECMO) to adequately

oxygenate and ventilate the blood while allowing the lung to rest remains an attractive strategy for the management of patients with acute lung injury, but has not been supported by clinical outcome studies. There is little apparent future for this technique in adult patients with ARDS. ECMO is best regarded at this time as heroic salvage therapy for patients with isolated respiratory failure in whom all other supportive measures have failed.

*Inhaled Nitric Oxide:* Nitric oxide (NO) is a potent endogenous vasodilator which, when given by inhalation, selectively vasodilates the pulmonary circulation. Inhaled NO (iNO) has several potentially salutary effects in ARDS: it selectively vasodilates pulmonary vessels which subserve *ventilated* alveoli, diverting blood flow to these alveoli (and away from areas of shunt). The first effect, the lowering of the pulmonary vascular resistance, accompanied by a lowering of the pulmonary artery pressure, appears maximal at very low concentrations (approximately 0.1 ppm) in patients with ARDS. The beneficial effects on oxygenation take place at somewhat higher inspired concentrations of NO (1-10 ppm). The rapid inactivation of iNO via hemoglobin binding prevents unwanted systemic hemodynamic side effects, but also mandates the continuous delivery of gas to the ventilator circuit. In the numerous studies evaluating the acute response to iNO, there has been a consistent finding of approximately 50% to 70% of patients improving oxygenation. However, two recent prospective trials have failed to demonstrate improved long-term outcome from iNO administration in ARDS ventilation, and thus this remains a salvage therapy at best.

## Circulatory Management of ARDS

Debate has surrounded the proper circulatory management of patients with ARDS for decades. On the one hand, animal and some clinical studies suggest that edemagenesis can be reduced by reducing pulmonary microvascular pressures in acute lung injury, in a fashion similar to the management of cardiogenic pulmonary edema. Of course, since these microvascular pressures are normal in these patients despite their lung flooding, the possibility of reducing cardiac preload exists, thus engendering inadequate organ perfusion in a patient population known to be at risk of multiple organ failure and indeed in whom outcome appears dictated in large part by the accrual of organ failures.



In addition, the proper monitoring tools for assessing the adequacy of the circulation in these patients and whether monitoring should include invasive hemodynamic measurement is equally controversial. It seems reasonable to state that mere monitoring with invasive measurements that is not coupled to a strategy to achieve pre-defined goals is not warranted.

It is difficult to make firm recommendations in the current state of knowledge. The ARDSnet is currently conducting a trial which enrolls and randomizes patients to management with either a central venous catheter or right heart catheter, and then each group is additionally randomized to receive a fluid liberal or fluid conservative strategy. It is hoped that information from this study will help guide the circulatory management of these patients and will determine how that strategy can be best conducted.

### **Management of Proliferative Phase ARDS**

A subset of patients with ARDS will progress over the first week of mechanical ventilation to disordered healing and severe lung fibrosis. This is usually characterized by increasing airway pressures or a falling  $V_T$  on pressure-control ventilation, a further fall in lung compliance, less response to PEEP, a “honey-comb” appearance on the chest radiograph, progressive pulmonary hypertension, and rising minute ventilation requirements (> 20 L/min). Barotrauma is a prominent feature and multiple organ failures often accrue. A number of observations regarding their supportive therapy should be made. Increased vascular permeability at this point in the course may be minimal, and strategies to reduce preload and edema are fraught with complications. Patients are prone to increases in Zone I lung conditions, and attempts to reduce the pulmonary capillary wedge pressure (Ppw) may result in increased dead space and hypoperfusion. Thus, seeking the lowest Ppw providing adequate cardiac output is no longer appropriate; instead, liberalization of fluid intake to provide a circulating volume in excess of that just adequate is a better strategy in this later phase of ARDS.

Interventions to directly influence the course of lung fibrosis are not well established but high-dose

corticosteroid therapy has its advocates. One recent prospective trial has shown an improved survival with the use of corticosteroids in late ARDS, but routine use in late ARDS remains controversial. The utility of corticosteroids in this setting will hopefully be determined by a trial currently underway under the auspices of the ARDSnet.

If corticosteroids are used in this setting, aggressive measures to monitor for ventilator-associated pneumonia are warranted. This complication of mechanical ventilation has a high incidence and high mortality in patients with ARDS. In view of the abnormal chest radiograph and gas exchange, multiple causes of fever and leukocytosis, and high incidence of colonization of the airway, diagnosis is difficult and may be aided by various techniques to obtain protected specimens.

### **Long-Term Sequelae of ARDS**

There is a variability to recovery of lung function following acute lung injury. Patients may recover with minimal or no abnormality by routine lung function testing shortly after acute lung insult, or they may remain substantially impaired for a year or longer, if not permanently. In most studies, approximately a fourth of patients show no impairment at one year, a fourth moderate impairment, roughly half only mild impairment, and a very small fraction severe impairment. Exertional dyspnea is the most commonly reported respiratory symptom, although cough and wheezing are common as well. A reduced single-breath carbon monoxide diffusing capacity is the most common pulmonary function abnormality. Spirometry and lung volumes tend to reveal mixed restrictive-obstructive abnormalities. Determining the prognosis after ARDS may be aided by obtaining complete lung functions at the time of discharge. Those patients with substantial abnormalities should be referred for appropriate follow-up. Herridge and colleagues also recently reported that lung dysfunction may be of only minor significance in terms of regaining general function, and that weight loss, neuromuscular weakness, and neuropsychiatric dysfunction related to critical illness or supportive management may be much more significant than respiratory dysfunction *per se*.

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## Notes

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