

# ARDS: Is There a Magic Bullet?

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## PATHOGENESIS OF ARDS

The acute respiratory distress syndrome (ARDS) is a devastating injury to the lungs, characterized by diffuse pulmonary inflammation, hypoxemia, and respiratory distress. Its mortality remains between 30% and 50%, despite early, aggressive and sometimes heroic intervention. Although in many cases complete recovery without sequelae is possible, in other cases ARDS may go on to a debilitating course requiring protracted ventilatory support, with high co-morbidity and mortality.

ARDS is usually considered as a homogeneous entity in standard definitions and in many large studies that evaluate therapeutic interventions. However, it should really be considered the final common pathway of a very heterogeneous group of insults. Although the injury is diffuse, it does not uniformly affect lung tissue and this nonuniform distribution has important therapeutic consequences. There are also two broad etiologies of ARDS. In *pulmonary* ARDS, there is a primary lung injury (e.g., pneumonia) that involves the alveolar epithelium and may be confined to single organ failure. In *extrapulmonary* ARDS, there is an insult—usually sepsis—at a remote location that reaches the capillary endothelium via a systemic inflammatory response syndrome, and lung failure becomes one more component of multisystem organ failure. Although there are important differences in pathophysiology, outcome between ARDS of pulmonary and extrapulmonary origin does not appear to differ greatly (1). The vast majority of studies reviewed here consider it as a single entity.

Whatever the insult, the acute inflammatory response in the lungs proceeds through two sequential phases: the exudative and the proliferative phase (2). Although these phases are pathophysiologically quite distinct, they may overlap temporally and even coexist in the same lung.

The exudative phase is characterized by acute alveolar epithelial injury, capillary leak syndrome, and alveolar and interstitial inflammation, and edema. Activated neutrophils liberate proteases, oxidants, and leukotrienes, and alveolar macrophages release cytokines such as tumor necrosis and interleukins. The alveoli become flooded with proteinaceous fluid that inactivates surfactant, and the basement membrane

becomes replaced by hyaline membranes. This culminates in diffuse alveolar collapse, intrapulmonary shunting and low ventilation-perfusion ( $V_A/Q$ ) ratios, with progressive lung stiffness and hypoxemia. Efforts to maintain the functional residual capacity with airway pressure therapy such as positive end-expiratory pressure (PEEP) may be helpful in reversing hypoxemia.

The proliferative phase is characterized by repair, resolution, and scarring. Alveolar edema fluid is resorbed; macrophages phagocytose intra-alveolar protein and apoptotic neutrophils; and type II pneumocytes undergo metaplasia to fibroblasts. At this stage resolution and healing may occur, or fibrosis may become dominant. Alveolar integrity may be restored, but the capillary network is progressively destroyed. This culminates in increasing dead space, high  $V_A/Q$  ratios, and progressive hypercarbia. Airway pressure therapy with PEEP becomes progressively less effective and may exacerbate  $\text{CO}_2$  retention.

## CLINICAL FEATURES

In 1994, the American-European Consensus Conference on ARDS condensed the clinical features of this syndrome into a definition that forms the basis for all the investigation since performed (3). Its criteria are 1) acute respiratory distress; 2) bilateral radiographic pulmonary infiltrates; 3) hypoxemia, defined as acute lung injury if the  $\text{PaO}_2$  to  $\text{FiO}_2$  (P:F) ratio is  $<300$ , or ARDS if  $<200$ ; and 4) the absence of heart failure, as defined by a pulmonary artery occlusion pressure (PAOP)  $<18$  mm Hg.

This definition is far from perfect. Respiratory distress, characterized by tachypnea, dyspnea, and acute respiratory alkalosis not relieved by correcting hypoxemia, is common to many pulmonary processes. Bilateral radiologic infiltrates may be caused by cardiogenic edema, pneumonitis, and several other entities. The P:F ratio may be influenced by therapy, especially PEEP and the  $\text{FiO}_2$  itself. It seems specious to separate “acute lung injury” from ARDS, when the former is in fact responsible for the latter. Heart failure may be present at PAOP  $<18$  mm Hg and may coexist with ARDS. Nonetheless—although presently undergoing revision—this definition has stood the test of time and

forms the basis for all investigation done on ARDS in the past decade.

## STRATEGIES FOR THE MANAGEMENT OF ARDS

### Conventional Therapy (1970–1995)

It was recognized as long ago as 1969 that survival in ARDS is predicated on the ability to maintain alveolar patency by the administration of PEEP (4), facilitated by early tracheal intubation and mechanical ventilation. Over the next two decades, this provided the mainstay of therapy, combined with efforts to decrease extravascular lung water by assiduous diuresis. The practice of combining large tidal volumes (10–12 mL/kg) with high levels of PEEP (10–25 cm H<sub>2</sub>O) culminated in very high airway inflation pressures (40–100 cm H<sub>2</sub>O).

Clinicians frequently encountered the entity of pulmonary barotrauma (pressure-induced injury), which at the time was accepted as an unavoidable consequence of the management of ARDS. Excessive distension of injured alveoli causes rupture of their walls, resulting in tracking of air through the interstitium (pulmonary interstitial emphysema). This may give a false impression of an “improving” pulmonary opacification on chest radiograph. The pleural membrane is tougher than the alveolar membrane, which delays the onset of overt pneumothorax, but this may occur at any stage during this process. Pulmonary interstitial emphysema tracks to the mediastinum (pneumomediastinum), thence to the subcutaneous tissues of the neck and thorax (subcutaneous emphysema). Ultimately, air may even track via the diaphragm to the peritoneal cavity (pneumoperitoneum), creating a false impression of subdiaphragmatic air as seen in perforation of a viscus.

An essential breakthrough in our understanding of ARDS was made by Luciano Gattinoni in Milan, Italy, using computed tomography (CT) scanning (5). He demonstrated that consolidation in ARDS is nonuniform, and that there are heterogeneous areas of diseased and near-normal lung, and that the latter has the dimensions of a child’s lung (“baby lung”). He further went on to show that a great deal of the lung injury induced by high airway pressures is due to excessive pressure (barotrauma) or distension (volutrauma) of the residual normal lung tissue. In this context, lung stiffness is also not uniform, with the “baby lung” having normal compliance for its size.

Subsequently, Gattinoni characterized patients with “chronic” ARDS with marked proliferation and scarring (6). Their lungs are stiff but PEEP is ineffective because dead space ( $V_d$ ) is increased, leading to CO<sub>2</sub> retention. These patients develop multiple dependent lung bullae, have a very high (almost 90%) incidence of pneumothorax, double the duration of ARDS than their cohorts, and a high mortality (66%).

### Protective Lung Strategy

There is considerable evidence that progressive lung parenchymal injury is induced by excessive alveolar distension by large tidal volumes, and alveolar collapse in the absence of PEEP. The mechanism appears to be a cytokine-induced inflammatory response, now known as ventilator-induced lung injury.

The compliance (pressure–volume) curve of the lung is sigmoid-shaped, with a lower and upper inflection point. Below and above these points, the alveoli are collapsed or distended and stiff (large pressure increase results in minimal volume increase). Between these points, alveoli have the best compliance (small pressure increase results in large volume increase). Protective lung ventilation implies alveolar ventilation between these two inflection points, i.e., relatively small tidal volumes (to prevent alveolar hyperinflation) with moderate PEEP to prevent alveolar collapse (7).

### Low Tidal Volume Ventilation

In 1994, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) initiated a network of academic centers to promote multicenter clinical investigation of ARDS, known as the ARDS Network or ARDSNet. The first study examined the hypothesis that low tidal volume ventilation (6 mL/kg, plateau pressure <50 cm H<sub>2</sub>O) would result in better outcome than high tidal volumes (12 mL/kg, plateau pressure <30 cm H<sub>2</sub>O). (8) The trial was stopped after 861 patients were randomized, because of a significantly decreased mortality in the low tidal volume group (31.0% vs 39.8%,  $P = 0.007$ ). This approach has since become the paradigm for protective lung strategy. However, certain caveats remain. Would a significant difference have been achieved if more modest tidal volumes (8–10 mL/kg) had been chosen for the control group? Is a tidal volume of 6 mL/kg ideal for all patients and throughout the course of ARDS? Finally, there is evidence that low tidal volumes alone are not very effective in recruiting collapsed alveoli (see below).

### High Versus Low PEEP

ARDSNet subsequently addressed the question of the ideal PEEP to be provided with a low tidal volume strategy. They randomized 549 patients to “low” (mean 8.3 cm H<sub>2</sub>O) vs “high” PEEP (mean 13.2 cm H<sub>2</sub>O). Although the “high” PEEP group had improved P:F ratios and lung compliance, there was no difference in ventilator-free days or mortality (9). Again, there are several caveats. A recruitment maneuver was incorporated in the initial protocol but dropped after 80 patients (it had no impact) and the PEEP protocol was changed after 179 patients to enhance the difference between the two groups. The difference in PEEP between the two groups was based on its increment. In the “high” PEEP group, baseline was 12

cm H<sub>2</sub>O, and increased to 20 cm H<sub>2</sub>O at an Fio<sub>2</sub> of 0.6; in the “low” PEEP group these settings were 5 and 10 cm H<sub>2</sub>O, respectively. However, if an Fio<sub>2</sub> of 1.0 was required, the PEEP in both groups was increased to 24 cm H<sub>2</sub>O.

### Pressure Controlled Inverse Ratio Ventilation

Pressure controlled ventilation is a ventilatory mode that is time-initiated, pressure-limited, and time-cycled. This results in a square pressure wave that provides tight control of the inflation pressure, which equals the applied pressure control + PEEP. It also allows precise increase in the inspiratory time at the expense of expiratory time, i.e., increased inspiratory:expiratory (I:E) ratio, or inverse ratio ventilation (IRV). Mean airway pressure is substantially increased without an increase in peak airway pressure, which promotes alveolar recruitment while (theoretically) attenuating barotrauma and volutrauma.

With pressure controlled inverse ratio ventilation (PC-IRV), mean airway pressures are typically increased from <10 to between 20 and 30 cm H<sub>2</sub>O; inspiratory time from <0.5 s to between 1 and 4 s; and I:E ratio from 1:2 to between 1:1 and 3:1. Indeed, IRV may be considered an alternative (or adjunct) to PEEP in providing airway pressure therapy; during inspiration instead of expiration, and with constrained peak airway pressure.

To date, ARDSNet has not tested the hypothesis that PC-IRV results in a better outcome than standard volume limited ventilation. Moreover, IRV may result in inadequate exhalation time, air trapping, and in the generation of intrinsic PEEP (auto-PEEP). Excessive intrinsic PEEP may itself promote barotrauma and CO<sub>2</sub> retention. Hypercarbia occurring during PC-IRV may be improved by paradoxically *decreasing* the ventilator rate, to allow additional time for CO<sub>2</sub> elimination.

### Permissive Hypercapnia

In 1990, well before the formation of ARDSNet, Hickling reported retrospective data from New Zealand on improved outcome in severe ARDS with the combination of limited peak airway pressure (<40 cm H<sub>2</sub>O), low tidal volumes (4–7 mL/kg), spontaneous breathing during intermittent mandatory ventilation (IMV), and permissive hypercapnia (Paco<sub>2</sub> 38–158 mm Hg, pH 6.79–7.45) (10). No attempt was made to buffer the acidosis. Hickling subsequently reported similar results from a prospective study, which however was small (53 patients) and uncontrolled (11). Hospital mortality rate was significantly lower than that predicted by APACHE II scores (26.4% vs 53.3%, *P* = 0.004).

Gradual institution of permissive hypercapnia appears to be well tolerated, and may increase oxygen unloading at the tissues by right-shift of the hemoglobin dissociation curve. There is experimental evidence that hypercapnic acidosis attenuates activation of the proinflammatory gene regulator, nuclear factor-kappa-B

(NF-κB). However, hypercapnia can dramatically exacerbate pulmonary vasoconstriction (an indication for inhaled nitric oxide, see below). Although permissive hypercapnia has not been subjected to a large, randomized outcome trial, it has become an established component of protective lung strategy (12).

### Airway Pressure Release Ventilation

An alternate strategy of achieving alveolar recruitment with lung protection is airway pressure release ventilation (APRV), also known as invasive bilevel ventilation. In this mode a sustained (3–4 s) high airway pressure, the upper level of PEEP (20–30 cm H<sub>2</sub>O), is intermittently released for about a second to the lower level of PEEP (5–10 cm H<sub>2</sub>O), while allowing spontaneous breathing to occur throughout the cycle. This provides alveolar recruitment while restricting the peak airway pressure to the upper PEEP level, and can maintain oxygenation and ventilation at lower airway pressures than conventional ventilation (13).

This mode is useful in the transition from PC-IRV to ventilatory weaning with IMV or pressure support, but it has not been subjected to randomized outcome trials.

### The Open Lung Concept

As suggested previously, the use of low tidal volumes (6 mL/kg) is not very effective in recruiting collapsed alveoli. The open lung concept is based on achieving an ideally inflated lung, by opening up collapsed alveoli with an initial recruitment maneuver, followed by high levels of PEEP combined with low tidal volumes. The goal is to sustain ventilation between the lower and upper inflection points of the lung pressure–volume curve.

Papadakos in Rochester, NY, has been a strong advocate of the use of PC-IRV to achieve an “open lung” concept (14). He advocates an initial recruitment maneuver with PC-IRV (I:E 1:1 or 2:1) and PEEP of 10–20 cm H<sub>2</sub>O, to peak airway pressures of 40–60 cm H<sub>2</sub>O for 10–30 ventilator cycles. The PC is then adjusted to decrease the peak airway to the lowest that will sustain a stable tidal volume or oxygenation, usually 10–30 cm H<sub>2</sub>O below the recruitment maneuver.

Although the open lung concept has physiologic and experimental support, it too has not been subjected to large scale clinical outcome studies. Meanwhile, Gattinoni has coined the term “potentially recruitable lung” based on CT studies during lung recruitment with peak airway pressures of 45 cm H<sub>2</sub>O and PEEP varied from 5 to 15 cm H<sub>2</sub>O (15). He showed a dramatic variability in response of lung recruitment, from 0% to 50% among individual patients, and this correlated with the percentage of lung tissue in which aeration was maintained after the application of PEEP. Patients with the smallest recruitable lung had the



most severe ARDS, and Gattinoni advocates limiting PEEP in these patients to avoid hyperinflation of normal lung units.

### Prone Positioning

Prone positioning has enjoyed varying degrees of interest over the last 30 yr, with a recent resurgence. In about two-thirds of patients with ARDS, the prone position can induce transient or sustained improvement in oxygenation, usually about 20%–30%. Initially the improvement was considered to be primarily due to the development of dependent atelectasis. Turning the patient prone matches perfusion to previously nondependent and expanded lung zones. Subsequently it has been suggested that improved chest wall mechanics and increased end-expiratory volume play an important role.

Although it requires skilled nursing and very close attention to patient safety, prone positioning is attractive in that it requires no special equipment (although special beds have been developed), and became incorporated into the management of ARDS in many units. Gattinoni led a multicenter randomized trial on 304 patients to test the hypothesis that a predefined strategy of prone positioning for 6 h or more daily for 10 days would enhance survival in patients with ARDS (16). Although prone positioning significantly increased oxygenation on a daily basis, there was no difference in 10 days, ICU discharge, or 6 mo mortality rate.

### High Frequency Oscillation

High frequency oscillation (HFO) potentially provides lung protection in ARDS by avoiding alveolar distension and collapse (17). Oscillation is provided at rates of 180–900 cycles per minute, or 3–15 Hz (1 Hz = 60 cycles per minute or 1 cycle per second), with sub-dead space tidal volumes (0.1–0.3 mL/kg), high gas flow, and an active expiratory phase. During HFO there are multiple potential mechanisms of gas exchange other than direct ventilation, including convective transport, “pendelluft” (inter-regional to-and-fro gas flow), longitudinal dispersion, and diffusion (18). High levels of PEEP are necessary to support the mean airway pressure and maintain alveolar recruitment.

In the HFO ventilator an adjustable power control determines the amplitude of piston displacement and peak and trough pressure excursions ( $\Delta P$ ) above and below the mean airway pressure. The oscillation frequency (Hz) determines the time for piston displacement, thus a lower Hz will lead to larger bulk tidal volumes. Oxygenation is determined by the  $F_{IO_2}$  and mean airway pressure, whereas ventilation and  $CO_2$  elimination is determined by  $\Delta P$  and oscillation frequency (Hz). Occasionally it may be necessary to create a small endotracheal tube cuff leak to facilitate  $CO_2$  washout.

HFO provides a number of management challenges, including the necessity for a firm bed surface,

with increased risk of pressure injury, and difficulty in adequate hydration of inspired gas. Nonetheless, it has established itself as a ventilatory mode in pediatric ICUs and trauma units, where it facilitates ventilation in the presence of abdominal compartment syndrome and constrained lung volume (19).

Thus far, only one large randomized trial has compared HFO with conventional ventilation. After 2–4 days of conventional ventilation, 150 patients were randomized to HFO or PC-IRV (tidal volume 6–10 mL/kg) (20). Patients who received HFO had improved P:F ratios at 24 h, but there was no statistical difference in mortality, 37% vs 52% ( $P = 0.1$ ). Clearly there is a need for a large randomized trial where HFO is instituted at an early stage of ARDS.

### Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) for pulmonary support is provided via a veno-venous circuit (VV-ECMO) that creates an oxygenated circuit in parallel to the venous system. From an internal jugular cannula, venous blood is pumped through an extracorporeal membrane oxygenator and thence returned to the femoral vein. The goal is to oxygenate venous blood returning to the heart, which in turn enhances arterial oxygenation sufficiently to sustain tissue metabolism.

Initial studies, such as the U.S. ECMO trial (1974–1977) used ECMO with complete lung collapse, and dismal survival (9%). Over the next 10 yr, Gattinoni demonstrated the effectiveness of maintenance of low levels of lung ventilation (pressure limit 35 cm  $H_2O$ , rate 3–5/min), utilizing low flow VV-ECMO for  $CO_2$  removal (21). In his hands, this approach, termed low frequency positive pressure ventilation with extracorporeal  $CO_2$  removal (LFPPV-ECCO<sub>2</sub>R) was associated with a 49% survival in very severe ARDS (21). In survivors, lung function improved within 48 h. In a subsequent randomized study in the U.S., Morris compared LFPPV-ECCO<sub>2</sub>R with PC-IRV, using computerized protocols in 40 patients (22). There was no statistical significance in 30-day survival: 33% vs 42% ( $P = 0.8$ ).

ECMO is an expensive, complex, resource intensive modality that requires considerable expertise. There is high risk of major bleeding and coagulopathy, thromboembolism, stroke, sepsis, and multisystem failure. Large scale experience remains the purview of specialized centers, such as the University of Michigan at Ann Arbor (<http://www.med.umich.edu/ecmo/intro.htm>). In our hands, we have found VV-ECMO to be a life-saving intervention in selected patients with primary ARDS, especially ischemic-perfusion injury after double lung transplantation. A salutary outcome is predicated on good cardiovascular function, the absence of multisystem organ failure, and relatively rapid (<72 h) lung function improvement.

## Magic Bullets

The term “magic bullet” refers to a single intervention, which, it is hoped, will substantially alter the outcome of ARDS. Unfortunately, none such exists!

### Steroids

In the 1970s, experimental models of septic shock suggested that pharmacologic doses of methylprednisolone (MPS), 30 mg/kg, might suppress the inflammatory response and enhance outcome. In the 1980s, two large scale randomized trials demonstrated that this intervention had no survival benefit, and increased prerenal azotemia through increased protein catabolism (23,24). This, together with laboratory evidence that high-dose steroids impaired mitochondrial and leukocyte function and vasodilator prostaglandin synthesis, caused the intervention to fall into disrepute.

In 1998, Meduri published the results of a randomized, double-blind, placebo-controlled study on 24 patients with severe ARDS (25). Study patients were given “low-dose” MPS ( $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ , with a weekly taper) for a month, starting at day 7, to test the hypothesis that administration of steroids would prevent the transition from the exudative to the proliferative phase of ARDS. Patients who received MPS had improved lung function, no increased incidence of concurrent infection, and their 30-day mortality was 12% compared to 62% in controls. This sparked an enormous resurgence of interest in steroid “rescue” in persistent ARDS, especially with evidence that steroids decrease capillary leak, leukocyte adhesion, and the expression of pro-inflammatory genes via NF- $\kappa$ B(26).

ARDSNet tested this hypothesis in the aptly named LaSRS (Late Steroid Rescue Study) trial, in which 180 patients who met ARDS criteria at 7 days were randomized to placebo or IV MPS for 28 days (27). The MPS protocol consisted of a loading dose of 2 mg/kg, followed by 0.5 mg/kg every 6 h for 14 days, 0.5 mg/kg every 12 h for 7 days. Patients who received MPS had significantly improved oxygenation, lung compliance, ventilator-free days, vasopressor requirement, and a lower incidence of septic shock. However, they also had significantly worsened glycemic control, rate of relapse (28% vs 9%), 28-day mortality, especially if MPS was started >14 days after onset (44% vs 12%), and a much higher incidence of severe critical illness neuromyopathy. ARDSNet concluded that their results do not support the use of steroids for persistent ARDS. This study also provides a caveat: beware of quickly translating promising results from small preliminary trials to widespread clinical application.

### Partial Liquid Ventilation with Perfluorocarbon

Experimental and preliminary clinical studies demonstrated that the instillation of an inert perfluorocarbon (Perflubron) into lungs damaged by ARDS enhances gas exchange and lung compliance and stabilizes alveoli as “liquid PEEP” (28). The liquid is

instilled via the endotracheal tube to a volume equivalent to the functional residual capacity to ensure that the lungs are completely filled during expiration only, allowing the entry of gas during inspiration (partial liquid ventilation, PLV). However, instillation is tedious and repetitive and contraindicated in the presence of a pleural leak, because the inert liquid is eliminated very slowly and may increase barotrauma.

In multicenter, prospective, controlled trial, 90 adult patients with early ARDS were randomized to receive PLV or conventional mechanical ventilation for a maximum of 5 days (29). There were no significant differences in ventilator-free days or mortality (42% vs 36%,  $P = 0.63$ ). Transient, self-limited episodes of hypoxia, respiratory acidosis, and bradycardia occurred more frequently in the PLV group. Based on these data, further large scale studies of PLV were abandoned.

### Inhaled Recombinant Surfactant Protein-C

Endogenous pulmonary surfactant phospholipids interact with surfactant proteins A, B, and C to lower alveolar surface tension. A role for exogenous surfactant administration has been established in the prevention and treatment of neonatal respiratory distress syndrome, which is characterized by immature surfactant production. In ARDS, surfactant is denatured and production is impaired. After preliminary studies of exogenous surfactant administration showed some promise, a large scale trial of intratracheal instillation of recombinant surfactant protein C-based surfactant was conducted in 448 patients with early (<48–72 h) ARDS (30). Although there was a significant initial improvement in oxygenation in the study group, there was no difference in ventilator-free days or mortality.

### Inhaled Nitric Oxide

Inhaled nitric oxide (INO) in concentrations of 1–40 ppm induces a selective and dose-dependent decrease in elevated pulmonary vascular resistance (PVR); it is rapidly scavenged by hemoglobin so it does not enter the systemic circulation. The decrease in right ventricular (RV) afterload provided enhances RV end-diastolic volume and ejection fraction. In the U.S., INO is approved only for the treatment of persistent pulmonary hypertension of the newborn (persistent fetal circulation), but has become established in the perioperative management of cardiac transplantation and left ventricular assist devices (31).

There are several ways in which INO might be beneficial in ARDS. It may decrease the pulmonary hypertension frequently encountered in ARDS, and facilitate permissive hypercapnia by preventing or reversing the increase in PVR induced by elevated  $\text{Paco}_2$ . When inhaled, nitric oxide is carried to areas of the lung with best ventilation, where it vasodilates the pulmonary circulation and improves ventilation-perfusion matching. Arterial oxygenation may improve as much as 20% in about 60% of patients, but unlike the effect

on pulmonary vasoconstriction, the benefit to oxygenation is quite variable, and may differ markedly between patients and even at different times in the same patient. Also, unlike the effect on PVR, there appears to be a “plateau” oxygenation response that reaches a maximum at 5–10 ppm. This may represent diffusion of NO to less well-ventilated lung units where it would tend to reverse hypoxic pulmonary vasoconstriction.

Although in individual cases of severe ARDS, INO may provide striking improvement in oxygenation, there is no evidence that it improves overall mortality. In a large multinational European trial, 268 adults with acute lung injury in 43 hospitals, who had a P:F ratio of <165, were treated with INO (32). Of these, 180 exhibited a positive response (>20% improvement in  $P_{aO_2}$ ), and were then randomized to no INO or INO at 2, 10, and 40 ppm. Although patients treated with INO had a significantly decreased incidence of severe ARDS (2.2% vs 10.3%), there was no difference in the primary end point, reversal of acute lung injury, or 30-day mortality (44% vs 40%). Because of these and other data, INO therapy is not advocated for the treatment of ARDS in the U.S.

### Circulatory Support

It is essential to provide adequate circulatory support to patients with ARDS. In the presence of a large intrapulmonary shunt, low cardiac output (CO)—for example, induced by overzealous diuretic therapy—may actually worsen oxygenation. Let us take the hypothetical example of a patient with a CO of 6 L/min and a 50% shunt, i.e., 3 L/min blood is oxygenated and 3 L/min shunted. Oxygenated blood leaving the lungs will have a maximal hemoglobin saturation of 100%, whereas shunted blood will be unchanged from the mixed venous saturation ( $S_{vO_2}$ ) at 75%. Equal mixing in the pulmonary veins results in a net saturation of 87.5%, equivalent to a  $P_{aO_2}$  of about 55 mm Hg. If the CO declines to 3 L/min, it is likely that  $S_{vO_2}$  will also decline because of increased tissue oxygen extraction. If the  $S_{vO_2}$  declines to 50%, the net effect of mixing in the pulmonary veins would be a saturation of 75%, equivalent to a  $P_{aO_2}$  of about 40 mm Hg. In patients who are hemodynamically unstable with low filling pressures, it is prudent to defer diuretic therapy and judiciously optimize preload. If filling pressures are normal or high, and tachyarrhythmias are not a limiting factor, it may be very helpful to augment CO with an inotropic agent such as dobutamine.

Recently, ARDSNet conducted large scale trials on the hemodynamic and fluid management of patients with ARDS. First they compared the impact of hemodynamic management guided by pulmonary artery catheterization (PAC) versus that guided by central venous pressure (CVP) monitoring alone (33). They found no difference in ventilator-free days or mortality between the two groups. There was also no significant difference in the per catheter complication rate

(0.06%–0.08%) between the two groups; the PAC group had twice as many arrhythmias but it was not documented how many were transiently related to PAC flotation. ARDSNet concluded that the PAC should not be routinely used in the management of acute lung injury. However, there are some important caveats. The study excluded all patients with an existing PAC in place, and those who had chronic obstructive pulmonary disease, severe renal injury, myocardial infarction, or liver disease. Of a total of 10,100 patients screened, only 1000 met study criteria and were enrolled in the study. Thus, we still do not have evidence for or against the use of the PAC in a potentially large proportion of patients with ARDS who are hemodynamically unstable or who have multisystem disease or dysfunction.

A concurrent study was done to compare a “liberal” versus “conservative” fluid strategy in patients with ARDS (34). Patients were managed with a PAC or CVP monitor, and were initially stabilized hemodynamically with pressors, inotropic agents, fluids, or diuretic therapy. They were assigned to a “liberal fluid” ( $PAOP < 8$  mm Hg,  $CVP < 4$  mm Hg) or “conservative fluid” ( $PAOP 14$ – $18$  mm Hg,  $CVP 10$ – $14$  mm Hg) regimen only when they were off pressors, had a cardiac index  $> 2.5$  L  $\cdot$  min $^{-1}$   $\cdot$  m $^{-2}$ , urine output  $> 0.5$  mL  $\cdot$  kg $^{-1}$   $\cdot$  h $^{-1}$ , and good peripheral perfusion. The results were that the patients in the liberal regimen group were net fluid positive about 7 L after 7 days compared with a zero net balance in the conservative regimen group. Patients in the conservative fluid group had improved oxygenation, increased ventilator-free, and ICU-free days, but there was no difference in overall mortality. ARDSNet concluded that their results support a conservative fluid strategy in acute lung injury.

In an accompanying editorial, Rivers emphasized that the study results should not be applied uniformly to patients with ARDS, who may go through an initial “ebb” phase, requiring fluid resuscitation, followed later by a “flow” phase, conducive to fluid mobilization. He also pointed out that patients in the study were already in the ICU more than 40 h, relatively young (average age 50 yr), stable or hyperdynamic and not in CHF or renal failure. These factors should be considered when applying any fluid regimen to any patient in an ICU!

### Some Final Thoughts and Caveats

#### Set Treatment Goals

An important first step in the treatment of ARDS is that the care team agrees on treatment goals for hypoxemia. A logical initial goal is to achieve a  $P_{aO_2} > 60$  mm Hg (equivalent to  $S_{pO_2} > 90\%$ ), because this is the upper inflection point of the hemoglobin dissociation curve—below this level, the saturation falls rapidly. Airway pressure therapy should then be directed to achieve the lowest  $F_{iO_2}$ —ideally,  $< 0.4$ —that will sustain a  $P_{aO_2} > 60$  mm Hg. If the  $F_{iO_2}$  cannot be



decreased, a further increase in airway pressure therapy is warranted, within the constraints described below. Once the  $\text{FiO}_2$  can be decreased to  $<0.4$ , and oxygenation is stable for at least 12 h, airway pressure may gradually be withdrawn. An important caveat is that too rapid withdrawal may result in alveolar derecruitment and collapse that may be very difficult to recoup. For example, PEEP should be withdrawn in decrements no greater than 2 cm  $\text{H}_2\text{O}$  every 6 h.

### Use a Step-Wise Combined Therapeutic Approach

From the discussion above, it may be concluded that no single intervention has been demonstrated to decrease mortality in ARDS, except use of low tidal volumes (but that is only in the context of comparing 6 mL/kg vs 12 mL/kg). Indeed, there are few comparisons of one intervention versus another. In one such study, Dupont et al. demonstrated that the prone position increased oxygenation (P:F ratio) more than INO therapy (35). However, Germann et al. took this one step further: they demonstrated that the combination of the prone position with INO therapy improved oxygenation more than either intervention used alone (36). Moreover, INO therapy also decreased PVR, whereas prone position had no effect.

A logical extension of these observations is that we should be examining combined therapeutic approaches and creating algorithms of therapy for ARDS, much like the evidenced-based guidelines included in the "Surviving Sepsis campaign" now advocated by the Society of Critical Care Medicine (37). One example is the report from the ICU group at the University of Vienna, Austria, a national referral center for ARDS, on a strictly protocol-based approach (38). All 84 of their patients were managed with a regimen that included sedation, early percutaneous tracheostomy, diuresis, continuous hemofiltration, and a step-wise treatment algorithm of PC-IRV, PEEP, permissive hypercapnia, INO therapy, and prone positioning. Nonresponders, defined as patients who did not exhibit a 20% increase in  $\text{PaO}_2$  within 96 h, were triaged to VV-ECMO. Their results are impressive: only 15% of patients required ECMO, and their overall survival rate was 80%; the survival rate in patients who went on to ECMO was 62%. There is a lesson to be learned here!

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