

# Nonventilatory Interventions in the Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome was first described in 1967. Acute respiratory distress syndrome and acute lung injury are diseases the busy intensivist treats almost daily. The etiologies of acute respiratory distress syndrome are many. A significant distinction is based on whether the insult to the lung was direct, such as in pneumonia, or indirect, such as trauma or sepsis. Strategies for managing patients with acute respiratory distress syndrome/acute lung injury can be subdivided into 2 large groups, those based in manipulation of mechanical ventilation and those based in nonventilatory modalities. This review focuses on the nonventilatory strategies and includes fluid restriction, exogenous surfactant, inhaled nitric oxide, manipulation of production, or administration of eicosanoids,

neuromuscular blocking agents, prone position ventilation, glucocorticoids, extracorporeal membrane oxygenation, and administration of beta-agonists. Most of these therapies either have not been studied in large trials or have failed to show a benefit in terms of long-term patient mortality. Many of these therapies have shown promise in terms of improved oxygenation and may therefore be beneficial as rescue therapy for severely hypoxic patients. Recommendations regarding the use of each of these strategies are made, and an algorithm for implementing these strategies is suggested.

**Keywords:** acute respiratory distress syndrome; acute lung injury; nonventilatory interventions

Acute respiratory distress syndrome (ARDS) was first described by Ashbaugh in 1967.<sup>1</sup> The syndrome is defined by criteria from the American-European Consensus Conference on ARDS.<sup>2</sup> Criteria for diagnosis include new bilateral pulmonary infiltrates and severe hypoxemia

(a PaO<sub>2</sub> to FiO<sub>2</sub> ratio <200) without evidence for congestive heart failure, including a pulmonary artery occlusion pressure ≤18. Although the PaO<sub>2</sub> to FiO<sub>2</sub> (P/F) ratio is a rough measure of disease severity, it does not predict mortality.<sup>3</sup> The incidence of acute lung injury (ALI), defined as a P/F ratio <300, and ARDS in the United States is approximately 17 to 64 per 100 000 person years. Mortality for ARDS is less than in past decades but still reported as ranging from 25.5% to 58%.<sup>4</sup>

The underlying pathophysiology of ARDS includes an inhomogeneous distribution of severe pulmonary injury of noncardiac origin. Pulmonary edema forms as a consequence of the initial injury and may predominate in the lung interstitium or within the alveoli.<sup>5</sup> There are many etiologies of ARDS. Common causes are sepsis, pneumonia, aspiration, trauma, pancreatitis, multiple blood transfusions, smoke or toxic gas inhalation, and drug toxicity.<sup>6</sup> In most research studies involving ARDS, these differing etiologies are included together. There may, however, be a differing response to certain treatments depending

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on whether the lung injury is a direct insult, such as aspiration or pneumonia, or secondarily induced, as in sepsis or trauma.

Numerous studies have focused on the methods of mechanical ventilation in ARDS, with recent enthusiasm for low tidal volume ventilation to reduce ventilator-induced lung injury. This is based on a recent study by the ARDS network.<sup>7</sup> Other available ventilatory treatment modalities have not been universally recognized as beneficial in this patient population. It is our goal to review those therapies, both pharmacologic and nonpharmacologic, that may be used as adjunctive treatment in ARDS. For this review, we performed MEDLINE searches for nonventilatory strategies that are currently in use in the United States. Papers addressing each therapy are reviewed, the methodology discussed, and recommendations formulated.

## **Acute Respiratory Distress Syndrome and Fluid Management**

Fluid management in patients with ARDS/ALI is complex because there are many physiologic code-terminants of lung edema. The balance of forces affecting net fluid flux across the pulmonary capillary barrier is governed by the Starling equation:  $Q_f = K_f[(P_c - P_{IF}) - \Omega(\Pi_c - \Pi_{IF})]$ , with  $Q_f$  = net fluid flux,  $K_f$  = filtration coefficient,  $P_c$  = capillary hydroc

fluid administration, diuretics, or a dobutamine drip was instituted. All patients in the study were ventilated using low tidal volume, volume-cycled ventilation. Pulmonary artery catheters were not associated with improved outcomes as measured by survival, ventilator days, or ICU days. They did result in more than twice as many catheter-related complications mainly related to arrhythmias.<sup>15</sup>

The homogeneity of the patient population in this study does limit its applicability to those patients addressed in the study, of which two thirds were those with ALI/ARDS of primary lung origin. Two thirds of these patients were also in the medical ICU, where fluid balance can be adjusted without regard to issues, such as blood loss or drains, often found in surgical and trauma patients. The current recommendation based on this recent literature would be to pursue a conservative fluid strategy in patients who have a primary lung injury and with no other indication for a more liberal fluid administration strategy. A PAC is not necessary for the management of these patients.

## Exogenous Surfactant

Pulmonary surfactant is an essential component of normal lung function.<sup>17</sup> The original function attributed to surfactant was the improvement of surface tension at the air-liquid interface and the prevention of alveolar edema.<sup>18</sup> Surfactant has also been shown to protect against bacterial and viral infections.<sup>19</sup> In vitro evidence suggests an ability to inhibit interleukin-1, interleukin-6, and tumor necrosis factor from human macrophages.<sup>20</sup> Outcomes of patients with ARDS have also been correlated with composition of aspirated surfactant.<sup>21</sup> Surfactant is composed of 90% lipids and 10% surfactant-associated proteins. Composition is remarkably conserved across species.<sup>22</sup> For these reasons, tested surfactant therapies have included both animal surfactants, synthetic surfactants, and recombinant protein-based surfactants.

Bronchoalveolar lavage (BAL) fluid from both patients with ARDS and patients with normal lungs who have been mechanically ventilated for prolonged periods has shown alterations in surfactant composition.<sup>23,24</sup> These alterations may be due to changes in type II pneumocyte metabolism, type II pneumocyte injury, or lytic activity within the airspaces.<sup>25</sup> Studies have examined the efficacy of exogenous surfactant in patients with ARDS. These

studies are heterogeneous in terms of the etiology and severity of lung injury, type of surfactant used, time schedule of administration, method of administration, and mode of ventilation used.<sup>18</sup>

Studies of surfactant therapy performed in the 1980s and early 1990s involved only small groups of patients but were able to demonstrate improvements in gas exchange.<sup>26,27</sup> Weg and colleagues<sup>28</sup> studied 51 randomized patients. There was improvement in oxygenation but no statistically significant trend toward improved mortality. Exogenous surfactant in large pediatric groups was also able to demonstrate improved oxygenation.<sup>29,30</sup> A small study used administration of a natural bovine surfactant directly in the airways. Patients were placed in multiple small groups based on dose given. Only the mid-level dose group showed a nonsignificant trend toward improved mortality.<sup>31</sup> All of these early studies used natural surfactants generally by the inhaled route. Anzueto and colleagues<sup>32</sup> performed one of the largest studies using inhaled synthetic surfactant in 1996. This synthetic surfactant has the advantage of containing surfactant proteins A, B, C, and D, whereas the natural surfactant mixtures contain mostly surfactant proteins B and C with some variability in the relative amounts of these proteins. In total, 364 of 725 patients with ARDS were randomized to receive continuous inhaled synthetic surfactant. No differences in mortality, oxygenation, or ventilator-free days were observed.

Recent studies published in 2003-2004 used bronchoalveolar lavage with a synthetic surfactant in ARDS patients. Gregory et al<sup>33</sup> reported a small, randomized, uncontrolled pilot study in which 22 patients received escalating doses of synthetic surfactant. Those patients receiving the highest doses fared better, with 100% alive and off mechanical ventilation at day 28, allowing for continuation of the study. Most recently in 2003 and 2004, Spragg and colleagues<sup>34,35</sup> reported on phase I/II and III clinical trials with a recombinant surfactant protein C-based surfactant. In the phase I/II study, patients were grouped according to dose used (high, low, control). Although there were dose-dependent trends toward improved oxygenation, decreased plasma and BAL IL-6, and improved survival at 28 days, none of these reached statistical significance. In the phase III study, 448 patients were randomized to surfactant administration or placebo up to 4 doses within 24 hours. Although there was significant improvement in oxygenation with surfactant treatment

initially, this difference was lost by 48 hours. There was improved survival in surfactant-treated patients with direct lung injury (ie, pneumonia or aspiration). When the total population was considered, however, the number of ventilator-free days as well as survival was not different between groups.

Exogenous surfactant in the treatment of ARDS cannot be routinely recommended at this point, but surfactant administration may yet prove beneficial. Future studies may help determine the composition, dose, route of administration, timing of administration, and patients who will benefit from surfactant therapy.

## Inhaled Nitric Oxide

Nitric oxide (NO) is synthesized from L-arginine, nicotinamide adenine dinucleotide phosphate (NADPH), and oxygen by the action of nitric oxide synthetase (NOS). Nitric oxide was originally described in the early 1980s as the compound previously known as endothelium-derived relaxing factor (EDRF), and inhaled nitric oxide (iNO) was first described for the treatment of ARDS in 1989.

When delivered by inhalation, NO distributes only to well-ventilated alveoli. Inhaled NO leads to vasodilatation by activating guanylate cyclase to induce the relaxation of vascular smooth muscle. This results in increased perfusion, leading to improvement in ventilation-perfusion mismatch.<sup>36</sup> This improvement in oxygenation has been documented in several well-designed studies. The response rate is less than 50% in septic patients<sup>37</sup> but 60% to 100% in nonseptic patients.<sup>36,38</sup>

The improvement in oxygenation appears within minutes and can be seen with doses as low as 0.1 ppm of nitric oxide. The majority of patients will have an improvement in oxygenation with doses of 20 ppm or less, although rarely 40 ppm is required.<sup>39</sup> Beyond 60 ppm, the response is unpredictable, and oxygenation may deteriorate. Dosages beyond 60 ppm are not recommended. As a result of the improved oxygenation, adequate arterial oxygenation could be achieved with lower FiO<sub>2</sub> and lower inspiratory airway pressures.

Patients with ARDS tolerate iNO well,<sup>36</sup> and prospective open-label randomized multicenter phase III trials have shown no increase in adverse effects.<sup>40</sup> There are no known significant risks associated with the use of iNO, although there have

been reports of worsening preexisting left ventricular failure (LVF) during iNO in New York Heart Association LVF grade III and IV patients.<sup>41</sup>

Inhaled NO is broken down by rapid combination with hemoglobin to form methemoglobin. This is normally reduced to functional hemoglobin and NO. The plasma half-life is 0.46 seconds, which explains the lack of systemic effects of iNO. Patients with congenital or acquired methemoglobin reductase activity may be an exception.

When compared to placebo-treated patients, iNO led to improvements in oxygenation within the first 4 hours. However, after 24 to 48 hours, the difference in oxygenation was lost. The data on long-term outcome—in particular, when survival, length of ICU stay, and ventilator-free days are the main outcome measures—have not shown any advantages to the use of iNO.<sup>38</sup> Results have been disappointing both in retrospective and prospective studies, despite temporary improvement in oxygenation and pulmonary artery pressure (PAP) (and right ventricular function).<sup>38,40,42</sup> Also, the use of iNO is associated with significant cost—estimated at \$3000/day in our institution in 2002.<sup>43</sup>

Overall, iNO works well as an additive for oxygenation improvement along with other adjuvant therapies (prone position, high-frequency ventilation, and prostacyclin). There is level I evidence that iNO provides short-term oxygenation improvement and reduction in pulmonary artery pressures, but there is no evidence of long-term benefits. Inhaled NO is therefore not standard treatment in ARDS and can only be recommended as a rescue therapy in ARDS patients with nonresponsive, life-threatening hypoxemia or as an alternative to extracorporeal membrane oxygenation (ECMO).

## Prostaglandins

Arachidonic acid is cleaved from plasma membrane phospholipids by the action of phospholipase A<sub>2</sub> to form prostaglandins. Prostaglandins have short half-lives and are inactivated after oral administration, therefore requiring continuous intravenous administration or aerosolization for effective administration. In patients with severe ARDS, prostaglandins reduce pulmonary arterial hypertension and redistribute pulmonary blood flow to ventilated segments of lung, with improvement in ventilation/perfusion matching and, therefore, in oxygenation.

## Alprostadi-Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>)

PGE<sub>1</sub> works mainly as an arterial vasodilator and a platelet aggregation inhibitor. Numerous studies have evaluated the role of PGE<sub>1</sub> in patients with severe ARDS, with administration by different methods: continuous intravenous infusion, intermittent boluses, liposomal formulation, or inhalational preparation.

The acute effects of PGE<sub>1</sub> are decreases in mean pulmonary artery pressure (MPAP), mean arterial pressure (MAP), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR). It also increases cardiac index (CI), oxygen delivery (DO<sub>2</sub>), and oxygen consumption (VO<sub>2</sub>). These effects are secondary to pulmonary arterial vasodilation, leading to reduced right ventricular afterload and increased cardiac index.<sup>44</sup>

In early clinical trials, Holcroft and collaborators<sup>45</sup> demonstrated improved pulmonary function in patients treated with PGE<sub>1</sub> as compared to placebo—with improved 30-day survival—although improvement in overall survival did not reach statistical significance. In a randomized, double-blind clinical trial, Abraham et al<sup>46</sup> showed that liposomal PGE<sub>1</sub> can lead to improvement of PaO<sub>2</sub>/FiO<sub>2</sub> ratio (PFR), but this did not translate into improved survival or reduced time on the ventilator.<sup>46</sup> Meyer et al<sup>47</sup> demonstrated that inhaled PGE<sub>1</sub> was an effective therapeutic option for improving oxygenation in patients with acute lung injury but could not demonstrate increased survival.

More recently, the TLC C-53 ARDS Study Group, in a multi-institutional controlled randomized study, was able to demonstrate improved oxygenation index with a liposomal formulation. Despite improved oxygenation, the treated patients had no change in the duration of mechanical ventilation and 28-day survival.<sup>48</sup>

None of the studies involving PGE<sub>1</sub> has shown any impact on major outcome measures such as survival or duration of mechanical ventilation, despite a favorable profile for secondary outcome measures.<sup>49-52</sup> PGE<sub>1</sub> is a useful adjunct to improve oxygenation in patients with severe ARDS but does not lead to improved survival. When administered intravenously, it must be given by central venous access, and patients must be monitored for hypotension, tachycardia, and bleeding.

## Epoprostenol-Prostacyclin (PGI<sub>2</sub>)

Prostacyclin has a shorter half-life than PGE<sub>1</sub>; it is synthesized by vascular endothelial and smooth muscle cells and causes direct vasodilation of the systemic and pulmonary vasculature in a dose-dependent manner, resulting in reduction of right and left heart afterload.

Animal studies suggest a benefit of intravenous PGI<sub>2</sub> in acute lung injury with improvement in PAP, PVR, and CO but no significant improvement in oxygenation.<sup>53</sup> In human studies, Domenighetti et al<sup>54</sup> were able to demonstrate differing responses in oxygenation and hemodynamics depending on the etiology of ARDS: Nebulization with PGI<sub>2</sub> was ineffective or worsened gas exchange in patients with ARDS of primary pulmonary origin, whereas there was improvement in patients with indirect ARDS. In primary ARDS, PGI<sub>2</sub> worsens the shunt because it is not selectively delivered to alveoli and can improve blood flow through the consolidated lung, whereas in indirect ARDS, PGI<sub>2</sub> reaches more accessible alveolar areas because the consolidations are less distributed (mainly gravity dependent; this explanation was reinforced by the computed tomographic [CT] number frequency distribution).

With PGI<sub>2</sub>, the observed physiologic effects have not led to improved clinical outcomes, and there still remains a potential for worsening of gas exchange. There are currently no national or international guidelines for the use of PGI<sub>2</sub>.

## Thromboxane Synthase and 5-Lipoxygenase Inhibitors

Thromboxane A<sub>2</sub> (TxA<sub>2</sub>) can initiate microvascular thromboses consisting of neutrophils and platelet aggregates that are responsible for perfusion abnormalities and recurrent ischemia reperfusion injuries to the lung. The vasoconstrictive effect of TxA<sub>2</sub> similarly contributes to impaired gas exchange.

The role of leukotrienes (LTs) in ARDS has been less well researched, but BAL fluid from patients with ARDS contains increased amounts of LTB<sub>4</sub>, LTC<sub>4</sub>, and LTD<sub>4</sub>, which may be markers for developing ARDS. Treatment with ketokonazole, an imidazole antifungal agent that inhibits thromboxane synthase and 5-lipoxygenase without inhibiting cyclooxygenase (COX), has a dual role of inhibiting

synthesis of inflammatory eicosanoids and directing COX products down less inflammatory metabolic paths such as those synthesizing prostacyclin or PGE<sub>2</sub>.

The ARDS Network trial KARMA (Ketokonazole and Respiratory Management in Acute Lung Injury and Adult Respiratory Distress Syndrome) found no difference in in-hospital mortality, ventilator-free days at day 28, organ failure-free days, and markers of gas exchange.<sup>55</sup> This adequately powered trial did not demonstrate a reduction of thromboxane production *in vivo*—the effect of decreasing thromboxane synthesis in ARDS is therefore still unknown.

## Neuromuscular Blocking Agents

Neuromuscular blocking agents (NMBAs) are routinely used in 98% of ICUs in the United States.<sup>56</sup> Up to 20% of patients with ARDS receive NMBA to facilitate mechanical ventilation and as an adjunct to treatment.<sup>57</sup> Neuromuscular blocking agents are given to eliminate spontaneous breathing, promote mechanical ventilation, and decrease oxygen consumption. They may also be used for certain forms of nonphysiologic mechanical ventilation, such as patients undergoing HFOV (high-frequency oscillatory ventilation) and IRV (inverse ratio ventilation), and to prevent respiratory compensation in patients managed with hypercapnic acidosis. Despite widespread use of NMBAs, there are few publications on the effects of NMBAs and gas exchange.

The theoretical mechanisms by which NMBAs improve oxygenation include the following:

1. reduction of oxygen consumption (in normal individuals at rest, O<sub>2</sub> consumption is 3% to 5% of total blood flow; in ARDS, it may increase to as much as 24%<sup>58,59</sup>);
2. facilitation of mechanical ventilation by preventing spontaneous respiratory movements in patients fighting the ventilator because of abnormal rates or cycling times; and
3. increased chest wall compliance with improvement in alveolar ventilation. This is accompanied by a reduction of peak airway pressures because of improved chest wall compliance and prevention of nonsynchronized spontaneous respirations with the potential to reduce barotrauma.

Numerous reports have described the use of NMBAs to facilitate mechanical ventilation. Most of these reports are limited to case studies, small prospective open-label trials, and small randomized

open-label and double-blind trials enrolling a wide variety of critically ill patients. None of these reports compared NMBAs to placebo.<sup>57</sup>

Garnier and coworkers,<sup>58</sup> in a multicenter, controlled, and randomized trial, demonstrated improved oxygenation (ie, improved PFR) and decreased positive-end expiratory pressure (PEEP) in patients treated with NMBA for 48 hours. Marik and Kaufman<sup>60</sup> demonstrated in critical care patients in respiratory failure that the use of neuromuscular paralysis decreases whole-body oxygen consumption, presumably by eliminating the work of breathing, resulting in a redistribution of blood flow from the respiratory muscles to the splanchnic and other nonvital vascular beds. Vernon and Witte<sup>61</sup> demonstrated a statistically significant decrease in oxygen consumption and energy expenditure in paralyzed, mechanically ventilated children.

In a retrospective case-controlled study in a pediatric population, Wilson and Jiao<sup>62</sup> observed an improved oxygenation index within 48 hours after cessation of NMBAs. They hypothesized that improvement in functional residual capacity (FRC) and less ventilation/perfusion mismatch was the cause of this improvement in oxygenation.

Some argue that many of these same effects can be obtained with deep sedation without all the risks of the NMBAs. Bruder et al<sup>63</sup> noted no added benefit of paralyzing agents in the oxygen delivery/consumption in patients adequately sedated. There is no documented improvement in respiratory mechanics or oxygenation compared to deep sedation alone. However, in critically ill patients, it is not always possible to eliminate all respiratory efforts with the use of hypnotic agents alone without hemodynamic compromise.<sup>60</sup>

On the other hand, increasing arterial oxygenation saturation has never translated to improvements in clinical outcome. Garnier et al,<sup>58</sup> in their study, despite improved oxygenation, were not able to demonstrate significant improvement in clinical outcomes. The use of NMBAs can be associated with significant risks, including increased incidence of critical illness myopathy—critical illness polyneuropathy (CIM-CIP), resulting in delayed weaning, increased risk of mortality from disconnection from the ventilator, and pressure ulcers.

Freebairn and colleagues,<sup>64</sup> in a placebo-controlled crossover trial in critically ill patients, were able to demonstrate improved respiratory compliance but no change in intramucosal pH, oxygen

consumption, oxygen delivery, or oxygen extraction ratios.

There are no randomized prospective trials that support the use of NMBA in the management of patients with ARDS.<sup>57</sup> They can be useful in terms of facilitating certain forms of mechanical ventilation. When required to facilitate mechanical ventilation, NMBA should be used judiciously with close monitoring consisting of frequent neurological examination, continuous monitoring of vital signs, and train of four (TOF) monitoring. Consider daily interruption and reevaluation of the need for paralysis. A rational utilization of NMBA may reduce the incidence of complications such as CIP-CIM.

### Prone Position Ventilation

It has long been appreciated that changes in body positioning will alter lung volumes and pulmonary mechanics. Piehl and Brown<sup>65</sup> were the first to report on improved oxygenation in prone patients with severe respiratory failure due to ARDS. More than 10 years later, in 1988, Langer and colleagues<sup>66</sup> provided a mechanism for the improvement in oxygenation in humans by demonstrating resolution of posterior lung densities detected by CT scanning when patients were turned to the prone position. Animal studies showed that this improved oxygenation may have been due to improved V/Q matching in dorsal lung regions, whereas ventral regions demonstrated unchanged V/Q matching.<sup>67</sup> Other investigators have proposed reduced lung compression by the heart as a mechanism for improved oxygenation.<sup>68</sup> Pelosi and colleagues<sup>69</sup> found improved oxygenation without favorable changes in pulmonary mechanics. In their study, worsening chest wall compliance correlated with improved oxygenation, implying that reducing chest wall compliance results in improved oxygenation. Although these studies have added to our understanding of the effects of prone positioning (PP), no one theory completely explains the change in oxygenation observed during PP or predicts which patients are likely to respond.

Ward<sup>70</sup> reviewed the literature regarding PP in ARDS and found improved oxygenation in 75% of subjects. Criteria for improved oxygenation, however, were variable, with PaO<sub>2</sub> and P/F ratio being the most commonly measured. The timing, duration, and schedule of PP have also been variable among the majority of studies of PP.<sup>71-73</sup> Duration of PP varied from 15 minutes to more than 20 hours.

Some studies used single events, whereas others used 2 or more PP trials.<sup>71-73</sup> Criteria for study entry and endpoints also varied; if patients were turned prone on multiple occasions, data were not always collected with each PP. All of these factors make for difficult analysis of these small studies, all less than 40 patients.

The first of 2 large randomized controlled trials to assess mortality effects of PP in ARDS were published in 2001.<sup>74</sup> Gattinoni and colleagues<sup>74</sup> randomized 304 patients to either a PP protocol or supine ventilation. Patients were assessed daily, and if criterion was met, they were turned prone for at least 6 hours that day. Ventilator management was at the discretion of the attending physician. Primary outcome measures were mortality at the end of 10 days, survival to ICU discharge, and survival at 6 months. Despite significant improvements in all oxygenation parameters, the mortality rate did not differ between groups at any of these time points. The tidal volumes used in both groups at baseline, however, were significantly higher than what is now considered acceptable. In a post hoc analysis, mortality was lower at 10 days and at ICU discharge if patients were turned prone and were in the lowest quartile for the P/F ratio, the highest quartile for Simplified Acute Physiology Score II, or the highest quartile for tidal volume. These benefits did not persist at 6 months.

Although only in abstract form, Mancebo and colleagues<sup>75</sup> reported on 136 patients randomized to prone or supine ventilation. This study was stopped early for reasons that were not made clear when a small but not statistically significant difference in ICU mortality was found in favor of PP. Guerin and colleagues<sup>76</sup> published a similar but larger study in 2004 of 791 patients with hypoxemic respiratory failure, including but not limited to ARDS and ALI patients. These patients were randomized to either supine or periodic prone ventilation. Twenty-eight-day mortality was the primary endpoint with 90-day mortality, ventilator-associated pneumonia (VAP), oxygenation, and duration of mechanical ventilation as secondary endpoints. Approximately 50% of each group was made up of ALI/ARDS patients. Prone positioning was for at least 8 hours per day and was stopped when fixed improvement criteria were met. Although oxygenation improved significantly and the rate of VAP was lower, there were no differences in 28-day mortality, 90-day mortality, or other measures. Most recently, Voggenreiter and colleagues<sup>77</sup> reported on their

protocol, which randomized 40 chest trauma patients who met criteria for ALI or ARDS to either supine or prone ventilation. These patients were stratified by chest and head abbreviated injury score and were kept in the prone position from 8 to 23 hours per day. The P/F ratio improved significantly in the prone group when compared to the supine group. Rate of progression from ALI to ARDS and incidence of pneumonia were also reduced in the prone group. However, there was no difference in mortality or days of mechanical ventilation between groups.

Prone positioning represents an extreme of patient positioning as a therapeutic modality in the treatment of ARDS. The potential to effect similar changes without complete inversion of the patient has also been studied using specialized beds that allow for continuous axial rotation of the patient. In a study by Bein and colleagues,<sup>78</sup> 10 patients who met criteria for acute lung injury or ARDS had parameters measured after 20 minutes of rotational therapy and 20 minutes after returning to a supine position. Oxygenation, as measured by the P/F ratio, was significantly improved during the period of continuous rotation, whereas the remainder of the measured ventilatory and blood gas parameters remained unchanged. It was also determined that V/Q mismatch improved significantly during the period of rotation. Staudinger and colleagues<sup>79</sup> randomized 26 patients with ARDS not due to trauma to either prone positioning or continuous rotational therapy. With initiation of positioning therapy, P/F ratio and shunt fraction improved equally in both groups. Although these results need confirmation in larger studies, continuous rotational therapy may represent an alternative to PP. Rotational therapy may also reduce the risk of malpositioned tubes and lines.

Based on all of the available data to date, PP or rotational therapy cannot be recommended as adjuncts in the treatment of ALI or ARDS. Prone positioning can be considered but is not recommended for rescue therapy as it has not been well studied for this specific indication and probably never will be on a large scale.

## Glucocorticoids

Acute respiratory distress syndrome is a diffuse inflammatory process resulting in an end-stage fibro-

proliferative response in the lung. Glucocorticoids are well-known inhibitors of these two processes, and there has been much interest in their therapeutic use in ARDS. Plasma cortisol levels have been correlated with severity of illness, severity of injury, and risk of death in several studies of trauma and ICU patients.<sup>80,81</sup> Although the significance of a normal serum cortisol in these patients remains unclear, Annane and colleagues<sup>82</sup> have shown that a lower response, less than a 9- $\mu\text{g}/\text{dL}$  increase in serum cortisol level, to an adrenocorticotrophic hormone (ACTH) stimulation test (250  $\mu\text{g}$ ) (nonresponders), correlated with increased mortality in patients with septic shock.<sup>82</sup> This group followed this with a randomized study that showed a mortality benefit to 7 days of low-dose cortisol replacement in this group of patients.<sup>83</sup> This group also performed a post hoc analysis of their data to examine the contributing effects of ARDS in their study patients.<sup>84</sup> This post hoc analysis demonstrated ARDS to be an important simultaneous diagnosis if mortality benefit is to be realized in treating these patients with steroids. Mortality at 28 days, ventilator-free days, and P/F ratio were all significantly improved in nonresponders who also met criteria for ARDS and received steroid replacement. There was no mortality benefit in patients who did not meet criteria for ARDS or were ACTH responders. There is no convincing evidence of benefit to patients with ARDS without vasopressor-dependent severe sepsis.

In 1987, Bernard and coworkers<sup>85</sup> reported on their experience with a short course of high-dose corticosteroids in the early stages of ARDS. Ninety-nine patients were randomized in 7 centers to either 30 mg per kg of methylprednisolone or placebo every 6 hours for 4 doses. Patients with both direct and indirect causes for ARDS were included, and patient groups were similar at entry. Of the outcome measures examined—including mortality at 45 days, chest radiograph criteria, blood gas criteria, shunt fraction, thoracic compliance, and arterial-alveolar gradient—none were significantly different between groups. The study was stopped early because it was initially designed to demonstrate a 25% reduction in mortality, which would have been impossible even with full enrollment, leaving open the possibility of a small benefit to corticosteroid therapy.

Four moderately sized trials either directly or indirectly examined the progression to ARDS in sepsis under the influence of corticosteroids.<sup>86-89</sup> The largest of these trials was by Bone and colleagues,<sup>88</sup>



who randomized 304 patients with a diagnosis of sepsis based on clinical criteria. Treatment patients received methylprednisolone 30 mg/kg every 6 hours for 4 doses. There was a nonsignificant trend toward an increased incidence of ARDS. The 3 other above studies all had fewer than 100 patients, and all showed either similar or increased progression to ARDS with no change in mortality when patients were treated with corticosteroids.

Meduri and coworkers<sup>90</sup> examined the benefits of a prolonged steroid course in the later stages of ARDS. Twenty-four patients with ARDS who had failed to improve after 7 days based on lung injury score were included. Sixteen patients were randomized to a prolonged course of methylprednisolone. The remaining 8 were randomized to placebo. Patients were allowed to blindly cross over to the alternative therapy if there was no improvement within 10 days of initiation of therapy. The study was terminated when a statistically significant reduction in ICU mortality was found in

ECMO from 1989 to 2003. Sixty-seven percent were weaned successfully from ECMO, and 52% survived to hospital discharge. All these studies suffer from similar weaknesses: They are retrospective, nonrandomized, and have varying inclusion criteria.

A randomized controlled clinical trial is currently enrolling patients to determine if advances in ECMO technology result in improved survival compared to best-available conventional therapy. As of July 1, 2005, 138 patients have been enrolled in the CESAR (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) trial.<sup>101</sup> At the present time, ECMO cannot be recommended as standard therapy in severe ARDS. Once the results of the CESAR trial become available, a more firm recommendation regarding ECMO can be made.

## Beta-Agonists

Beta-agonists, through a variety of effects, have the potential to improve outcomes in patients with ALI/ARDS. These potential mechanisms include prevention of neutrophil sequestration in alveoli, increased neutrophil apoptosis, shifting the balance of production of inflammatory mediators to anti-inflammatory mediators, increased production of surfactant components by type II pneumocytes, and reduced epithelial damage by certain bacteria.<sup>102</sup> Perhaps most intriguing and most well studied of the effects of beta-agonists in humans with ARDS are the beneficial effects on clearance of lung water and improvement in lung mechanics. In 10 patients with ARDS who were treated with terbutaline, Basran and associates<sup>103</sup> showed decreased plasma protein extravasation and accumulation in the alveolar space. Several studies have demonstrated an increase in dynamic compliance in ARDS patients,<sup>104-106</sup> whereas at least 1 study has also demonstrated increased static compliance by an unknown mechanism.<sup>104</sup> Much work remains to determine the role of beta-agonists in ARDS. However, in vitro experimental data and several clinical studies show some promise.

## Conclusions

Several of the nonventilatory strategies for the treatment of ARDS have been explored in randomized multicenter trials enrolling large groups of ARDS patients. None of these modalities has been proven

universally beneficial when mortality is considered as the outcome variable. This does not necessarily prove the lack of efficacy of these therapies. Rather, these therapies are unsuccessful in the particular group of ARDS patients studied. Also, certain therapies may provide other benefits by reducing ventilator or ICU days, which should translate into cost savings. Although these therapies cannot be routinely recommended, some subsets of patients may benefit from these strategies either as routine therapy or as rescue therapy. Other adjunctive treatments have not been studied in large trials, and decisions regarding their use must be made on the currently limited available data. Extracorporeal membrane oxygenation is currently undergoing study in a prospective fashion, and data regarding efficacy of this therapy may soon be available.

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