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# Pediatric Acute Hypoxemic Respiratory Failure: Management of Oxygenation

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**Acute hypoxemic respiratory failure (AHRF) is one of the hallmarks of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), which are caused by an inflammatory process initiated by any of a number of potential systemic and/or pulmonary insults that result in heterogeneous disruption of the capillary-pithelial interface. In these critically sick patients, optimizing the management of oxygenation is crucial. Physicians managing pediatric patients with ALI or ARDS are faced with a complex array of options influencing oxygenation. Certain treatment strategies can influence clinical outcomes, such as a lung protective ventilation strategy that specifies a low tidal volume (6 mL/kg) and a plateau pressure limit (30 cm H<sub>2</sub>O). Other strategies such as different levels of positive end expiratory pressure, altered inspiration to expiration time ratios, recruitment maneuvers, prone positioning, and extraneous gases or drugs may also affect clinical outcomes. This article reviews state-of-the-art strategies on the management of oxygenation in acute hypoxemic respiratory failure in children.**

Key words: *pediatrics, acute respiratory distress syndrome, acute lung injury, oxygenation, acute hypoxemic respiratory failure, ventilator-induced lung injury*

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Over the past 30 years, our understanding of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), ventilator-induced lung injury (VILI), and the systemic inflammatory response syndrome has greatly improved. Because acute hypoxemic respiratory failure (AHRF) is the hallmark of ALI and ARDS, the management of oxygenation is crucial in oxygen delivery and in limiting the local inflammatory reaction that can initiate or exacerbate a systemic inflammatory cascade.

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During oxygenation, arterial hemoglobin saturation is titrated upward to avoid the harmful effects of tissue hypoxia and downward to prevent the harmful effects of hyperoxia and lung injury induced by mechanical ventilation [1,2]. Traditionally, oxygenation strategies are developed by selecting and coordinating the most appropriate methods of ventilation and gas delivery. These strategies often involve identifying and using optimal levels of positive end expiratory pressure (PEEP), tidal volume, respiratory rates, and inspiration/expiration ratios. Recently, however, new strategies have been developed in the management of oxygenation. For example, lung-protective strategies for mechanical ventilation have been shown to improve oxygenation and reduce VILI. In addition, maneuvers with the ventilator (recruitment maneuvers) or altering the patient's positioning (prone positioning) can modify pulmonary dynamics and lower oxygen requirements. Also, certain gases (such as inhaled nitric oxide) or drugs with selective pulmonary vasodilator effects (such as almitrine) can alter pulmonary physiology, resulting in lower oxygen requirements.

This article reviews traditional and new strategies used in the management of oxygenation in AHRF and attempts to guide intensivists and pulmonologists in managing infants and children with acute respiratory failure.

## Definitions

AHRF was first described in 1967 in 12 adult patients [3]. Since then, the condition has been redefined twice and has been renamed acute respiratory distress syndrome (ARDS) [4,5]. The American-European Consensus Conference on ARDS (1992) introduced the latest and currently accepted definition of ARDS. Another more benign form of acute respiratory failure, termed ALI, has also been defined [5]. ALI and ARDS are defined as respiratory illnesses with an acute onset with the presence of bilateral infiltrates on chest radiogra-

phy and a documented pulmonary artery wedge pressure  $\leq 18$  mmHg (or absence of clinical evidence of left atrial hypertension). In ALI, the  $\text{PaO}_2/\text{FiO}_2$  ratio is  $\leq 300$ . In ARDS, the  $\text{PaO}_2/\text{FiO}_2$  ratio is  $\leq 200$ .

## Incidence

ARDS occurs in roughly 15 to 75 persons per 100,000 [6]. However, it is difficult to estimate the true incidence of ARDS in the general population because the disease is heterogeneous. In addition, prior to the American-European Consensus Conference, there was no uniform definition of ARDS. Clinical disorders that place patients at risk for ARDS can be divided into those associated with direct injury to the lung (primary ARDS) and those that cause indirect lung injury (secondary ARDS) in the setting of a systemic process [7]. Sepsis is associated with the highest risk of progression to ALI or ARDS in adults [8].

## Mortality

Despite technical and medical advances in the past 30 years, the mortality rate associated with ARDS in adults has remained greater than 50% until recent years, as survival statistics from individual centers have begun to indicate that outcomes may be improving [1,8-10]. However, no single factor explains this reduction in mortality. Review of the pediatric literature suggests similarly improved prognosis for ARDS in infants and children, with reported mortality rates as low as 10% to 30% [11-15].

Most deaths in adult and pediatric ARDS patient populations are attributed to sepsis or multiorgan failure. Few patients with ARDS die from pulmonary gas exchange failure and isolated hypoxemia. However, recently, ventilation strategies that presumably minimize VILI have been used successfully to reduce mortality, suggesting that lung injury may be indirectly related to death in ARDS [1,16-18].

The data on outcomes in pediatric AHRF, unlike adults, is more difficult to interpret. A recent study screened all mechanically ventilated (for more than 24 hours) pediatric patients younger than 18 years who were admitted to 9 large pediatric intensive care units (ICUs) in North America over 6 consecutive winter months [15]. They found that only 6% of 6403 admissions to these pediatric ICUs were potentially eligible for clinical studies of therapies

for acute respiratory failure. ARDS was diagnosed at study entry in only 7.6% of the patients. The median length of mechanical ventilation support was 11 days for ARDS patients and 6 to 7 days for patients ventilated for other acute pulmonary diagnoses. Although underlying oncologic diagnoses were uncommon in the overall population (less than 3.3%), they were disproportionately represented in this group of ARDS patients (13%). Overall mortality was a rare event (1.6%), even for patients with a diagnosis of ARDS (4.3%). This is in sharp contrast to mortality reported from adult ARDS patients (30% to 50%). Furthermore, the duration of mechanical ventilation is relatively short, and the need for mechanical ventilation over 28 days is rare. The authors therefore suggest that the design of clinical trials in this population using traditional outcomes may be difficult as the population is heterogeneous, death is infrequent, and the average length of time on the ventilator is short. Certain groups of children, however, still appear to have a more dreadful mortality rate from ARDS. Specifically, immunocompromised children and those who have received bone marrow transplants have a 15% to 20% survival rate of AHRF [19,20].

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## Mechanical Ventilation Strategies

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### Protective Mechanical Ventilation Strategies

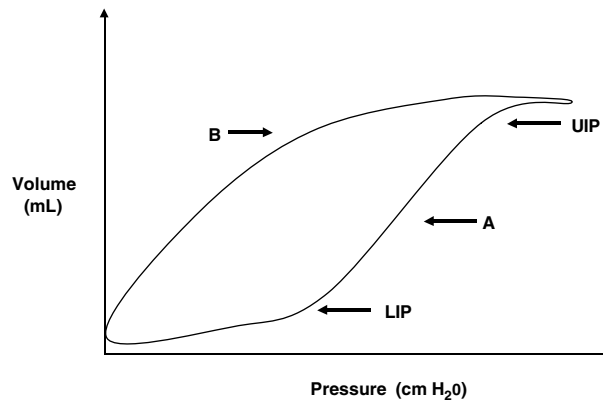
Mechanical ventilation increases the risk of VILI through 2 potential mechanisms: (1) overdistension of gas-filled alveoli and (2) the repetitive opening and closing of atelectatic alveoli [21-24]. In addition, the risk of lung injury from mechanical ventilation is higher because in ARDS, normal and diseased lung tissues are interspersed [9]. Results from animal studies suggest that mechanical ventilation that is inappropriately administered can injure lungs, causing VILI [25]. Soon after inappropriate mechanical ventilation is initiated, a cascade begins in which inflammatory cells infiltrate pulmonary structures and inflammatory cytokines in the lung begin to increase. The surfactant system then becomes damaged, and pulmonary edema develops [21,26]. These processes are remarkably similar to the inflammatory cascade seen in the lungs in the early stages of ARDS [24]. Because of these risks, ventilation of patients with AHRF remains controversial, and consensus on how to identify

optimal PEEP and tidal volume has not been achieved [27-30].

One method for trying to identify optimal PEEP and tidal volume is to measure the patient's pressure-volume curve [29,31-35]. The curve is obtained by measuring pressure changes in the respiratory system while the system is inflated in a stepwise fashion from end expiratory volume. The pressure-volume curve in ARDS typically has a sigmoidal shape with 2 inflection points: one is at low lung volume (termed the *lower inflection point*) and the other is at higher lung volume (termed the *upper inflection point*) (Figure 1). The lower inflection point is regarded as the opening pressure of the atelectatic, noncompliant, dependent alveoli [29]. Animal and human studies show that maintaining a PEEP above the lower inflection point improves gas exchange and protects against lung injury [17,22,24,36]. The upper inflection point is the point at which parts of the lung become overdistended, and it indicates a fall in lung compliance [37,38].

Inappropriate ventilation—using a PEEP below the lower inflection point or using a tidal volume above the upper inflection point—may cause a spectrum of pulmonary and systemic lesions. These lesions include air leaks as well as endothelial, epithelial, and tissue damage [22,23,39]. In addition, pulmonary and systemic inflammatory mediators can initiate an inflammatory cascade, leading to lung injury and a systemic inflammatory response [30,40]. On the other hand, appropriate mechanical ventilation reduces bronchoalveolar and plasma levels of proinflammatory cytokines and results in fewer distant organ failures [17,41]. Lung injury from mechanical ventilation is therefore thought to be minimized by using PEEP above lower inflection point and tidal volumes that maintain airway pressures below the upper inflection point. Alternatively, some animal studies have shown that ventilation occurs in the deflation limb of the pressure-volume curve. According to these studies, PEEP can be below the lower inflection point but above the closing pressure of the lungs, as determined by the deflation limb of the pressure-volume curve [42].

There are several methods of determining optimal PEEP at the bedside [38]. The first method attempts to delineate the patient's pressure-volume curve and is referred to as the "super-syringe" technique [38]. Following preoxygenation with 100% oxygen, the patient is removed from the ventilator circuit, and the lungs are allowed to deflate to expiratory reserve volume. The lungs are then reflat-



**Fig 1.** Pressure-volume curve of the respiratory system is typically sigmoidal in shape. It is composed of an inflation limb (A) and a deflation limb (B). There are 2 inflection points termed the *lower inflection point* (LIP) and the *upper inflection point* (UIP). Lung injury from mechanical ventilation is thought to be minimized by using positive end expiratory pressure above the LIP and tidal volumes that maintain airway pressure below the LIP.

ed with increments in volume using a large syringe with 100 to 1000 mL of 100% oxygen (dependent on patient size). A plot of pressure versus volume is recorded, and the optimal PEEP is set based on the resulting pressure-volume curves. A second method uses volume-controlled ventilation with a square waveform and low gas flow. The pressure-volume relationship is derived from data collected by flow and volume sensors connected to the ventilator, which is then used to determine the optimal PEEP. A third method is to initiate ventilation with low PEEP (often starting at between 7 and 10 cm of water) using a volume-control mode of ventilation with a square waveform, low flow, and a constant tidal volume. The optimal PEEP is the point at which, after gradual increments in PEEP, no further improvement in the respiratory compliance is obtained. A fourth method is similar to the third but uses a pressure mode of ventilation [38].

Recently, 5 prospective randomized controlled trials [1,16,43-45] comparing conventional (large tidal volumes, high peak inspiratory pressures, and lower PEEPs) and lung protective ventilation, that is, low tidal volume (6 ml/kg) and/or plateau pressure limit (usually less than 30 cm H<sub>2</sub>O), have been conducted. Three of these studies with a combined total of 288 patients demonstrated no advantage from this protective ventilation strategy [43-45]. However, 2 of these trials on adults with ARDS that included 53 [16] and 861 [1] patients have recently documented the effectiveness of using protective ventilation strategies to manage oxygenation. The

largest and most conclusive study to date supporting the effectiveness of using protective ventilation strategies is from the Acute Respiratory Distress Syndrome Network of the National Institutes of Health [1]. This multicenter randomized trial was stopped after 861 patients had been enrolled because mortality was significantly lower among patients receiving protective ventilation than those who were not (31% vs 39.8%, respectively;  $P = .007$ ). The use of the protective ventilation in this trial was a major breakthrough in how to safely use mechanical ventilation in patients who are critically ill with ARDS. Patients who received the conventional treatment were ventilated with an initial tidal volume of 12 ml/kg, with a plateau pressure of  $\leq 50$  cm of water. In contrast, patients who received protective ventilation were ventilated with an initial tidal volume of only 6 ml/kg, with a plateau pressure of  $\leq 30$  cm of water. Peak inspiratory pressures greater than 30 cm water were allowed in this group only if the tidal volume fell below 4 ml/kg, if the pH was below 7.15, or both. In the treatment group, the mean tidal volumes on days 1 and 3 were  $6.2 \pm 0.8$  and  $11.8 \pm 0.8$  per kilogram of predicted body weight ( $P < .001$ ), respectively, and mean plateau pressures were  $25 \pm 6$  and  $33 \pm 8$  cm of water ( $P < .001$ ), respectively. The study did not use pressure-volume curves to select the levels of PEEP but used a sliding scale of "allowable combinations of  $\text{FiO}_2$  and PEEP." The National Institutes of Health study offers convincing evidence that a strategy that limits VILI by minimizing tidal volume and peak inspiratory pressure reduces mortality in adult patients with AHRF. This study did not, however, determine whether pressure-volume curves can be used to determine optimal PEEP and did not determine if additional tidal volume goals (eg, 7, 8, or 9 ml/kg) are safe.

Our practice is to ventilate patients using a pressure mode of mechanical ventilation and to optimize PEEP either by analyzing individual pressure-volume curves or by selecting levels based on a sliding scale [1]. We maintain a tidal volume of between 4 and 6 mL/kg and advocate a peak inspiratory pressure of less than 30 cm water. Our goals are to maintain a pH greater than 7.20 and  $\text{FiO}_2$  less than 0.45. If necessary, boluses of tromethamine are given to patients whose serum pH is below 7.20.

### High-Frequency Oscillator Ventilation

High-frequency oscillator ventilation (HFOV) uses the excursion of an oscillator within the ventilator

circuit to generate rapid respiratory rate at very low tidal volumes [46]. Following the results of clinical studies on conventional ventilation that have shown the advantages of limiting tidal volume and maintaining lung volume, interest in HFOV has grown [47,48]. After adequate lung recruitment, the low tidal volume provided by the HFOV makes it possible to maintain the high lung volumes at a higher point on the pressure-volume curve with less risk of overdistension. Animal studies using HFOV have shown that compared to conventional ventilation methods [49-52], HFOV improved oxygenation and resulted in less lung damage. However, these benefits have not been easily replicated in humans [53-70].

For preterm and term neonates with AHRF, HFOV has been used as the primary method of mechanical ventilation [53-58]. The first large multicenter trial, which was conducted in the presurfactant era and without the use of lung recruitment, failed to produce better outcomes than conventional ventilation [54]. However, recent randomized controlled trials in these age groups [53,55-59] have shown that HFOV is now considered safe and effective. Despite this compelling physiological and clinical evidence, no one to date has demonstrated unequivocally that this method reduces mortality or the incidence of chronic lung disease [71].

As many as 33% of all older pediatric patients with AHRF (excluding newborns) receive HFOV at some point in their illness [64]. Those patients who do not respond to HFOV have a much higher risk of dying. Despite this, little data on outcomes or the use of this method as a primary mode of mechanical ventilation are available for this population as well. The use of HFOV has been shown to be safe and effective as a rescue mode in improving oxygenation in children with AHRF either when used alone [60,61,63-66] or in conjunction with nitric oxide [62]. Arnold et al used the randomized crossover design to study 58 older children with AHRF, 29 of whom were randomized to an HFOV treatment arm [60]. They found that over time, HFOV was associated with improvement in oxygenation. Although the study examined AHRF in children resulting from a variety of causes, 55% of these children met ARDS definition criteria. Those patients who were randomized to HFOV had better rank outcomes than the patients who were on conventional ventilation or those who crossed over to HFOV. Fedora et al have retrospectively studied the effect of early rescue intervention of HFOV on outcome in 26 consecutive pediatric patients with AHRF (mean age of 3.7

years) who at some point of their illness were treated with HFOV [63]. They found a significant difference in mortality: 58.8% of the early intervention patients ( $n = 17$ ) who were placed on HFOV within the first 24 hours of mechanical ventilation survived. Only 12.5% ( $n = 9$ ) of the late intervention patients who were placed on HFOV beyond 24 hours survived. Arnold et al also conducted a survey of 10 pediatric ICUs across the United States and found that pediatric patients (with and without preexisting lung disease) had an improved oxygenation index during initiation of HFOV [64]. They also found that several variables correlated with risk of mortality, namely, immunocompromise, sepsis syndrome, oxygenation index prior to institution of HFOV, oxygenation index at 12 and 24 hours after HFOV initiation, and the length of time patients were on conventional ventilation prior to initiation of HFOV. Although these studies were relatively small, it appears that early initiation of HFOV in pediatric respiratory failure is associated with better oxygenation and consequently, a better outcome.

In our pediatric practice, we use HFOV as a rescue therapy in patients with AHRF. The timing of its use varies among our group of intensive care physicians. If patients appear to require tidal volumes or peak inspiratory pressures greater than those recommended in the protective low-volume ventilation strategy, they are given a trial of HFOV. Once we ventilate patients in the HFOV mode, we use sustained inflation maneuvers to optimize lung volumes. Initial mean airway pressures are often 4 to 7 cm H<sub>2</sub>O higher than those previously used in conventional methods of ventilation. A frequency of 5 to 9 Hz is chosen for pediatric patients, with the lower range being used for older children. We select a  $\delta$  pressure, which produces an optimal chest wall “wiggle.”

### Inverse Ratio Ventilation

In contrast to conventional mechanical ventilation, in which the normal inspiration to expiration time ratio (I:E ratio) is 1:2 to 1:4, inverse ratio ventilation uses a prolonged inspiratory time, in which the I:E ratio is greater than 1:1 and often as much as 2:1. In theory, it leads to a higher mean airway pressure that reduces the shunt fraction at lower levels of PEEP and peak alveolar pressure [72]. Several studies comparing this method with conventional methods [73-75] show the potential risks inherent in the former. These risks include an increased need for sedation and a higher likelihood of gas trapping.

The latter leads to significant auto-PEEP, which can reduce cardiac output and systemic oxygen delivery and increase the risk of pneumothorax.

No large randomized controlled trial has compared the outcome of the inverse ratio ventilation strategy with conventional ventilation in either adult or pediatric patients. Several observational case series using historical controls have reported success with the maneuver in adults, but there are no reports in the pediatric literature [76,77]. We believe that the proper use of PEEP with sustained inflation avoids the need for this strategy.

In our pediatric practice, we use inspiratory times as long as 3 seconds when patients' arterial oxygenation is marginal despite optimal ventilation strategy. These patients require adequate sedation and paralysis.

### Recruitment Maneuvers

Several reports [78-81] have shown that lung atelectasis, which occurs during low tidal volume ventilation, can be prevented by large volume breaths even if they are delivered intermittently. Subsequently, lung recruitment maneuver (RM) began to be used, whereby sustained inflation pressures were used to recruit atelectatic regions of the lung to improve oxygenation [42,82-93]. The American-European Consensus Committee on ARDS (part 2) has proposed RM as an adjunct to the lung-protective strategy of ventilation to reverse lung atelectasis that is related to low tidal volume [88]. Recent studies suggest that lungs in secondary ARDS can be recruited more easily than in primary ARDS [87]. Even though RMs have been safely used in patients with AHRF [94], transient cardiopulmonary decompensation and air leak syndromes can potentially occur.

Various techniques have been used to provide RM, in particular, continuous positive airway pressure (CPAP) or intermittent sighs. In adults with ARDS, RMs that use high CPAP levels have been shown to improve oxygenation [16,84,94] and lung mechanics [16,84]. Amato et al used 40 cm H<sub>2</sub>O CPAP for 40 seconds, with PEEP set at 2-cm H<sub>2</sub>O above the lower inflection point, and observed an increase in the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, respiratory system compliance, and 28-day survival rate compared with controls [16]. However, they did not clearly describe the frequency of these maneuvers or the population of the patients that received RM. Recently, Grasso et al [84] applied 40-cm H<sub>2</sub>O of CPAP for 40 seconds in 22 ARDS patients while using the ARDSNet lung-protective ventilation strat-

egy; they observed a 50% increase in  $\text{PaO}_2/\text{FiO}_2$  ratio in half of the patients. The other half, whose  $\text{PaO}_2/\text{FiO}_2$  ratio increased by only 20%, had been ventilated for a longer period of time and showed a significant decrease in cardiac index and mean arterial pressure. The responder group also had a lower lung and chest wall elastance and had been ventilated for a shorter period of time with less hemodynamic impairment than the nonresponder group. Because the process of derecruitment is gradual after RM, it has been suggested that a sufficient PEEP level after RM should be applied as an effective strategy to prevent derecruitment [90].

Providing intermittent sighs [86] is another RM technique that involves delivering intermittent breaths of larger tidal volume, which are administered either via the mechanical ventilator or manually with a bag and mask. Sighs up to 45-cm  $\text{H}_2\text{O}$  plateau pressure have been used. This has been associated with markedly improved oxygenation and lung elastance. Although these intermittent sighs recruit collapsed alveoli, the benefit is usually short-lived.

Although RMs have been shown to improve oxygenation, none of the above studies have solidly demonstrated that these maneuvers improve outcome. There is also no agreement on the optimal level of pressure or the timing, duration, and frequency of these sustained inflations in patients with AHRF.

In children with normal lungs during anesthesia, RMs have been used to reverse atelectasis [93]. However, there have been no studies to our knowledge on the safety and efficacy of RMs as an adjunct in the management of pediatric patients with AHRF. To fill this gap, we are currently conducting such a study.

In our practice, we extrapolate from adult studies and use RMs during mechanical ventilation. We use continuous positive airway pressure of generally 20-cm  $\text{H}_2\text{O}$  pressure above the level of existing PEEP for 30 to 45 seconds on sedated and preferably muscle-relaxed patients. This maneuver is primarily carried out in the early stage of AHRF at least twice daily or more if required until it appears to no longer improve oxygenation (an increase in  $\text{PaO}_2$  of at least 10% to 20% within 30 minutes of the maneuver).

## Inhaled Vasodilators

Pulmonary vasodilator agents, which have been shown to improve oxygenation in patients with AHRF, include inhaled nitric oxide (iNO) and

prostacyclins. This review will focus only on the clinical use of iNO.

Nitric oxide (NO) is a free radical gas released constitutively in the lung by endothelial cells. It causes pulmonary vasodilation primarily via the secondary messenger cyclic guanosine monophosphate [95-98]. iNO therapy can decrease the occurrence of ventilation-perfusion mismatch [99], which is a characteristic feature of AHRF. It does this by selectively vasodilating blood vessels associated with ventilated alveoli. It also reduces the increased pulmonary vascular resistance commonly seen in AHRF [100]. This therapy also regulates both immune and inflammatory responses, decreases neutrophil sequestration in the lung, decreases edema formation, and regulates its own production [101-104]. iNO has few systemic effects due to the rapid and strong combination with hemoglobin to form methemoglobin. It also reacts slowly with oxygen and water to form toxic  $\text{NO}_2$ , nitrous and nitric acids, which can damage the lung at concentrations as low as 2 parts per million (ppm) [105,106]. However, the currently used iNO delivery system minimizes contact time and concentrations of the gases so that these toxic by-products are less likely to form within the ventilator circuit. iNO also interacts with superoxides to form peroxynitrites [105]. These have been shown in vitro to oxidize and nitrosylate proteins, nucleic acids, and lipids, including essential components of the surfactant system. The clinical significance of this peroxynitrite production is unknown.

The effect of iNO on oxygenation can frequently be seen in less than 10 minutes, although it can take as long as several hours [107,108]. iNO also lowers elevated pulmonary artery pressure in about 60% of patients with AHRF [109]. This improved oxygenation is seen in the dose range of 1 to 10 ppm of iNO. However, several trials have shown that the positive effect of iNO usually diminishes with time [108-111]. Doses of iNO greater than 80 ppm do not benefit patients and can increase the risk of toxicity.

We still do not know the predictors of an individual's response. Furthermore, intraindividual and interindividual responses to iNO therapy differ and also vary over time. Responses can be influenced by lung recruitment, coexistent pathology, or the resolution of inflammation. When patients do respond to iNO, they are weaned of it gradually. The last 1 to 2 ppm may have to be weaned especially slowly because "rebound" pulmonary hypertension and hypoxemia can occur.

In neonates (> 34 weeks) who have AHRF associated with pulmonary hypertension, iNO is a rec-

ommended standard therapy [112,113]. The Food and Drug Administration and the European Commission have approved its use because it has clearly been shown to decrease the need for extracorporeal membrane oxygenator (ECMO) in this population.

In older children and adults with AHRF, iNO improves PaO<sub>2</sub> and reduces pulmonary artery pressure in the acute phase of its application, if only temporarily [62,107,114-116]. However, it is not a part of standard therapy in this population because clinical reports suggest that it does not increase survival rates or the number of ventilator-free days, nor does it reduce the need for ECMO [117]. This therapy is used only as part of a rescue therapy to improve oxygenation in patients with AHRF and in those with impaired right ventricular function secondary to hypoxia-related pulmonary hypertension. Dobyns et al [116] conducted a placebo-controlled trial in which children were randomized either to iNO with conventional ventilation or to conventional ventilation alone for 72 hours. During the first 12 hours, oxygenation index was better in the iNO-treated patients. The effects, however, were short-lived. A post hoc analysis of the study showed that long-term oxygenation improved only in those patients with severe AHRF ("severe" was defined as a more profound disruption of oxygenation at presentation [oxygenation index  $\geq$  25]) or in immunocompromised patients.

As multiple therapies are simultaneously instituted in a critically ill patient with AHRF, it is difficult to evaluate the efficacy of iNO alone. Baldauf et al [114] evaluated 119 data points in 19 ARDS patients during the first 72 hours of iNO therapy. They found that in 42% of these data points, improvement in oxygenation was not due to iNO alone. The authors concluded that in most cases, oxygenation improves due to multiple therapies instituted simultaneously and not due to iNO alone.

In our practice, iNO is part of our standard care in newborns (> 34 weeks) with AHRF and in children with pulmonary hypertension associated with the operative repair of congenital cardiac defects that are unresponsive to other therapies. We also use iNO when transporting neonates and older children with severe AHRF from other care centers to our institution, if they are already on iNO. We offer iNO as part of a rescue therapy to older children with AHRF who would be considered for and meet the standard criteria for ECMO. In these children, we tend to perform an iNO trial to evaluate their responsiveness to this gas. An iNO trial involves evaluation of the response to 20 ppm of

iNO. If the PaO<sub>2</sub> does not improve by more than 20% after 30 minutes of iNO therapy, the treatment is discontinued.

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## Nonmechanical Ventilation Strategies

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### Prone Positioning

Prone positioning (PP), which was first proposed by Bryan in 1974 [118] and involves placing a mechanically ventilated patient in the PP, has been shown to improve oxygenation and lung mechanics, enabling ventilator support to be reduced in adult and pediatric patients with AHRF [119-128].

The mechanism by which PP improves oxygenation is not entirely clear. Although alveolar collapse is more predominant in the dorsal regions of the lung, PP appears to recruit these atelectatic dorsal regions of the lung. This makes the ventilation of the alveoli more uniform, improving ventilation-perfusion matching and thereby improving oxygenation. In addition, PP may also optimize the removal of secretions and postural drainage, which also improves ventilation-perfusion matching [129].

Studies have shown that PP improves oxygenation in approximately 70% to 80% of children and adults with AHRF [120,123,125]. The magnitude and duration of improvement from PP varies, possibly depending on the duration and distribution of lung injury at the time of positioning. PP is mostly used early in the acute phase of the ARDS after mechanical ventilation has been initiated, since the presence of fibrosis in late-stage ARDS can cause patients to be nonresponsive to it [122].

Although complications from PP are infrequent [130], oxygenation can worsen, and extubation or cardiac arrest can occasionally occur. Other complications include skin ulcers, pressure sores, eye injury, and dislodgement of venous or arterial catheters. Physical restrictions such as cervical collar and extensive abdominal surgery can also prevent the use of PP.

In children with AHRF, PP causes sustained improvement in arterial oxygenation [123-128]. In PP responders, this improvement in oxygenation is usually achieved within 2 hours after position change and can be sustained for a 12-hour period [123]. Casado-Flores et al [128] recently showed that when prone-supine/supine-prone postural changes were repeated every 8 hours (within  $56 \pm 109$  hours after the diagnosis of severe ARDS), oxy-

generation improved in 18 out of 23 pediatric patients. Even though no statistically significant difference was found for the mortality rate, it was higher for the nonresponders (80%) versus the responders (39%). Curley et al [123] investigated PP for 20 hours per day soon after identification and initiation of mechanical ventilation in 25 pediatric patients with ALI. Positive response to PP was defined as (1) more days of  $\geq 20$  mmHg increases in PaO<sub>2</sub>/FiO<sub>2</sub> ratio or (2) a  $\geq 10\%$  decrease in oxygenation index when the patient was shifted from a supine to a prone position during the study period. The authors differentiated between immediate responders (those who improved within 1 hour of PP), cumulative responders (those who improved over 1 to 19 hours of PP), and persistent responders (those in whom the response was maintained for 1 hour after being placed again in a supine position). Remarkably, overall, 84% of these patients responded positively to PP. As some of these responded to PP over 20 hours, the authors suggest that patients with ALI should be maintained in the prone position for a longer period of time to get a response.

In adults, improvement in oxygenation is similar to that found in children [119-122]. A large, multicenter, prospective, randomized study [122] failed to show any difference in mortality at day 10 in ARDS patients who were either randomized to PP for at least 6 hours a day or left in a supine position. However, subsequent analysis of the study results found that PP patients with the lowest PaO<sub>2</sub>/FIO<sub>2</sub> ratio at the beginning of the study ( $< 88$  mmHg) did have lower mortality (23%) after day 10 than did supine-positioned patients (47%).

In our practice, PP is not included in the general protocol for ventilation of patients with AHREF. However, we often place patients with persistent hypoxemia in the prone position. These patients are kept prone for 12 hours or more and are rotated between the prone and supine position until they no longer improve in oxygenation in the prone position.

### Corticosteroids

Because corticosteroids reduce the production of many inflammatory and profibrotic mediators that are associated with ARDS and ALI [131], they have been used in both adults [132-134] and children with these conditions [135,136]. Steroids are thought to be beneficial in treating ARDS that is caused by or co-occurs with steroid-responsive dis-

orders, such as *Pneumocystis carinii* pneumonia with HIV infection [137], acute eosinophilic pneumonia [138], and bronchiolitis obliterans organizing pneumonia [139].

The use of corticosteroids has been investigated in both the early ( $< 7$  days) [132] and the late ( $> 7$  days) [134,135] stages of ARDS. A number of trials have demonstrated that patients at risk of ARDS or with early ARDS (associated with sepsis) do not benefit from a short course of large doses of corticosteroids administered early in the disease [132,140,141]. In some of these studies, a higher mortality rate [133], a higher rate of infections, and a lower rate of reversal of ARDS were documented in the patients who received steroids [133,141]. However, in light of recent studies in patients with sepsis, it is still unclear whether ARDS related to sepsis would respond favorably to early steroid treatment. In septic patients, these randomized controlled studies using steroids early in the course of their disease reported lower mortality in the group treated with steroids compared to the placebo group [142,143]. These studies are in contrast to earlier studies in patients with sepsis, which reported no decrease in mortality.

In the late (fibroproliferative) stage of ARDS, low doses of steroids administered for longer terms have been suggested to be beneficial [134,144]. It is hypothesized that steroids may reduce the mediators of fibrosis in late-stage ARDS. A randomized controlled trial evaluated 24 patients in late ARDS. Sixteen patients were treated with methylprednisolone. The loading dose of 2 mg/kg was followed by a dose of 2 mg/kg per day for 2 weeks and then tapered down until day 32 of therapy [134]. Whereas 5 (out of the 8) patients originally given placebo in the nonsteroid group died, none of the patients in the steroid group died. Steroids clearly improved oxygenation and facilitated extubation. However, despite an aggressive protocol for monitoring and treatment of infections during this trial, 75% of patients in both arms of the trial developed new episodes of sepsis in addition to ARDS. To validate these results, the National Institutes of Health is conducting the ARDS Network Late Steroid Rescue Study, which will enroll 180 patients to study the effects of administering low-dose long-term steroids to patients in late ARDS. In summary, timing and duration of steroid therapy are likely to be of importance. A therapeutic window exists for treating late-stage ARDS. The treatment of late-stage ARDS with steroids will be ineffective once end-stage fibrosis has developed [145,146]. Furthermore, it appears that steroids decrease lung

collagen and edema production when used for prolonged periods, whereas stopping it rapidly negated these positive effects [147].

In children, what is known about the effects of steroids in either early- or late-stage ARDS is anecdotal and based on a few case studies [135,136]. Practitioners largely extrapolate treatment protocols from results reported in the adult literature.

In our pediatric practice, we administer steroids to children in late ARDS, by day 7 to 10 of mechanical ventilation, based on adult protocols [134].

## Surfactant

Surfactant, which is synthesized and recycled by type II alveolar cells, lowers alveolar surface tension and prevents collapse of alveoli at low lung volumes [148-150]. As a result, it reduces the net movement of fluid into the alveolar spaces. It also has anti-inflammatory and antimicrobial properties [151,152]. ARDS alters the biophysical properties of surfactant, contributing to the dysfunction of the lungs [153-155]. It has been suggested that exogenous surfactant improves oxygenation in these patients. Various preparations, doses, administration regimens, and delivery techniques have been proposed in adults and children [156-163].

Surfactant that is formulated with lipids and proteins has been found to improve oxygenation more effectively. Surfactant can be administered by intratracheal delivery, aerosolization in ventilator gas, and direct bronchoscopic instillation. Surfactant has no significant adverse effects. The size of the dose depends on the route of instillation. The optimal time and duration of surfactant therapy in AHRF is still unknown.

Children with AHRF were studied by Willson et al, who conducted a multicenter, randomized trial of a calf lung surfactant extract, calfactant [157]. This study enrolled 42 children with AHRF. The study showed that surfactant appears to be safe and caused rapid and sustained improvement in oxygenation. The group that received surfactant spent significantly less time on mechanical ventilation and had a shorter ICU length of stay, compared to the control group. However, there were no differences in mortality. The same number of patients in both groups went on to other therapies, such as ECMO and HFOV. Hermon et al conducted another retrospective study in 19 children with ARDS [158] and found that after the first dose of surfactant was administered, oxygenation improved. A multicenter trial is currently underway in the

United States to evaluate the effects of surfactant in children with AHRF.

Based on encouraging results from earlier phase I/II trials using recombinant surfactant protein C-based Venticute [156,161], adults with ARDS were studied recently in 2 large, simultaneous, phase III clinical trials. One was conducted in North America (n = 224) and the other in Europe/South Africa (n = 224). Surfactant significantly improved oxygenation in the treatment groups compared with the control groups in both trials, but other outcomes (ventilator-free days/survival rates) did not differ between the groups in the 2 trials. However, post hoc analysis of the data showed that patients with ARDS caused by pneumonia and/or aspiration had a lower mortality rate than did their respective control groups.

In our pediatric practice, we do not routinely use surfactant. We use it routinely in our neonates with hyaline membrane disease. When we do use it in older children, we use Survanta, an animal-based surfactant instilled via the endotracheal tube (doses = 6 cc/kg) in a trial to rapidly improve oxygenation when other conventional therapies were ineffective.

## Extracorporeal Membrane Oxygenator

ECMO is an adapted form of conventional cardiopulmonary bypass technique that allows lungs to rest while the body is being oxygenated. It has been used for treating AHRF in neonates, older children, and adult patients since the 1970s [164-176]. This technique is used when all other conventional measures fail to improve oxygenation.

Eighty percent of 10,391 AHRF neonates survived after treatment with ECMO, according to the ECMO Life Support Organization registry (report from 1980 to 1995) [177]. Tracy and Stolar reported that the cumulative survival rate in 982 older children with AHRF originating from diverse etiologies was 53% from 1990 to 1995 [177]. In a retrospective study, Morton et al reported a similar mortality rate of 54% in 28 children beyond the neonatal period; the recovery of lung function on day 7 of ECMO treatment was correlated with a good outcome [171]. Likewise, Green et al, in a retrospective multicenter cohort analysis of 331 pediatric patients, reported that patients who suffered from severe AHRF and were treated with ECMO had a reduced mortality rate [172]. This reduced mortality rate was seen in the sickest patient cohort, with a predicted mortality rate of 50% to 75%.

In adults, the use of ECMO still remains controversial. While earlier trials in the 1970s [166] on the effectiveness of ECMO reported very low survival rates (15%), recent reports have demonstrated that the survival rate of the sickest cohort of ARDS patients being managed on ECMO actually increased [175,176].

Even though ECMO can save some of the sickest children and adults, complications and long-term morbidities can arise. Factors that limit its use in pediatric patients are availability, the potential short-term (bleeding, oxygenator failure, circuit disruption, cannula-related complications, etc), and long-term (adverse neurologic outcomes, inability to wean off ECMO, etc) complications, and the high cost.

In our practice, we use EMCO on a case-by-case basis and not routinely. Candidates for ECMO therapy are usually rapidly deteriorating hypoxic patients for whom other methods of respiratory support have failed to improve oxygenation.

## Other Treatments

In addition to the treatment strategies described above, several additional alternatives are available to improve oxygenation in patients with AHRF. These include partial liquid ventilation, alternative modes of parenteral nutrition, almitrine infusion, and others. This review will not include a discussion on these therapies.

## Conclusion

Physicians managing pediatric patients with acute lung injury or ARDS are faced with a complex array of options influencing oxygen therapy. A tremendous body of knowledge has accumulated regarding the physiological, cellular, and molecular basis of respiratory failure and VILI. Decisions regarding mode of mechanical ventilation, selection of optimal levels of PEEP, tidal volume, I:E ratio, protective ventilation strategies, recruitment maneuvers, PP, and extraneous gases or drugs may all affect clinical outcome. Several attractive strategies have been shown to improve oxygenation and pulmonary physiology in lung injury. However, most of these strategies need rigorous testing before they are proven beneficial in improving patient outcome. To date, only a strategy of protective ventilation has emerged as an effective therapy in reducing mortality of patients with ARDS.

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