CME

Rescue Therapies for Acute Hypoxemic Respiratory Failure

Linda L. Liu, MD, J. Matthew Aldrich, MD, David W. Shimabukuro, MDCM, Kristina R. Sullivan, MD, John M. Taylor, MD, Kevin C. Thornton, MD, and Michael A. Gropper, MD, PhD

The recent H1N1 epidemic has resulted in a large number of deaths, primarily from acute hypoxemic respiratory failure. We reviewed the current strategies to rescue patients with severe hypoxemia. Included in these strategies are high-frequency oscillatory ventilation, airway pressure release ventilation, inhaled vasodilators, and the use of extracorporeal life support. All of these strategies are targeted at improving oxygenation, but improved oxygenation alone has yet to be demonstrated to correlate with improved survival. The risks and benefits of these strategies, including cost-effectiveness data, are discussed. (Anesth Analg 2010;111:693–702)

Acute lung injury (ALI)[1] and acute respiratory distress syndrome (ARDS) are devastating disorders affecting up to 200,000 patients each year in the United States.[2] Acute hypoxemia remains a major cause of morbidity and mortality in this patient population, and approximately 40% of these patients die. The recent pandemic of H1N1 influenza has resulted in >16,000 deaths worldwide* and has renewed interest in rescue therapies for hypoxemia. Recent studies[3–5] demonstrate that a larger percentage of hospitalized patients with either confirmed or presumed H1N1 will require admission to the intensive care unit (ICU),[6] most of whom will have severe respiratory failure. An observational study of H1N1 patients in the United States demonstrated a 25% ICU admission rate, with >60% of patients requiring mechanical ventilation.[4] Other recently completed studies of H1N1 patients in Canada and Australia/New Zealand demonstrated similar demand for critical care services with a high incidence of severe respiratory failure. Data from Australia and New Zealand revealed that >64% of patients admitted to the ICU with 2009 H1N1 required mechanical ventilation for a median period of 8 days.[5] A prospective observational study from Canada revealed that among 168 patients with confirmed or probable 2009 H1N1, >80% required mechanical ventilation for a median duration of 12 days.[5] Unlike most patients with ALI or ARDS, these patients are relatively young and present with severe respiratory failure/ARDS that is notable for often difficult to manage hypoxemia. Despite maximal support with modern treatment strategies including lung protective ventilation, prone positioning, inhaled pulmonary vasodilators, and high-frequency oscillatory ventilation (HFOV), a substantial percentage of H1N1 patients have demonstrated refractory hypoxemia and hypercarbia. In most patients with traditional ALI and ARDS,[5] oxygenation can be adequately supported using measures such as positive end-expiratory pressure (PEEP) or increasing inspired oxygen concentration. Because of the severe hypoxemia seen in these patients, there has been renewed interest in salvage therapies for severe hypoxemia. This review examines the currently available salvage therapies for ALI and ARDS, and the evidence supporting their use.

*Pandemic (H1N1) 2009: Update 90. Available at: http://www.who.int/csr/don/2010_03_05/en/index.html. Accessed March 7, 2010.

From the Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California.

Accepted for publication May 6, 2010.

Disclosure: The authors report no conflicts of interest.

Address correspondence and reprint requests to Michael A. Gropper, MD, PhD, University of California San Francisco, 505 Parnassus Ave., Room M917, San Francisco, CA 94143-0624. Address e-mail to gropperm@anesthesia.ucsf.edu.

DOI: 10.1213/ANE.0b013e3181e9c356

PROTECTIVE MECHANICAL VENTILATION

The current standard of care for ALI and ARDS is the use of protective mechanical ventilation. Although it is not the purpose of this review to provide a detailed discussion of lung protection, the ARDSNet trial, which compared lower tidal volumes (V_T) (6 mL/kg ideal body weight) to higher V_T (12 mL/kg ideal body weight) in patients with ALI, found a nearly 25% reduction in mortality.[7] Although not consistently applied in patients with ALI/ARDS, low V_T ventilation and limitation of inspiratory plateau pressures remain the most effective treatment. It must be remembered that in patients enrolled in the ARDSNet trial, Pao_2/fraction of inspired oxygen (Fio_2) was significantly higher in the first 3 days in patients randomized to higher V_T, yet these patients had higher mortality. Caution should be exercised, therefore, in assuming that an intervention that merely improves oxygenation will prove beneficial.

Low V_T mechanical ventilation minimizes lung stretch in an effort to avoid ventilator-induced lung injury, specifically barotrauma (lung injury from high pressure), volutrauma (lung injury from overdistention), atelectrauma (injury from cyclic collapse and opening of lung units), and biotrauma (lung injury from inflammatory mediator release). Intrinsic to a lung protection strategy is the understanding that most patients can tolerate permissive hypercapnia with accompanying mild acidosis. There are few strategies to improve oxygenation in patients undergoing protective mechanical ventilation: increase Fio_2, increase mean airway pressure by increasing PEEP, or

increase mean airway pressure by prolonging the inspiratory phase. If these simple interventions are unsuccessful in providing adequate oxygenation, then salvage therapies need to be considered.

LUNG RECRUITMENT MANEUVERS

Patients with ALI/ARDS have heterogeneous lung collapse resulting in shunt and ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching. Reexpansion or recruitment of collapsed lung units will improve oxygenation on a temporary basis. Rothen et al.[8] were the first to use computed tomography to demonstrate that recruitment maneuvers (RMs) restored atelectatic lung segments after general anesthesia. In 1992, Lichtwarck-Aschoff et al.[9] provided the first description of lung recruitment as a therapy for improved pulmonary function in an animal model of ARDS. In 1998, Amato et al.[10] conducted the first randomized controlled trial that incorporated RMs with a low V_T ventilation strategy. It was suggested at that time that RMs would positively affect outcomes based on improved oxygenation.

A common feature of RMs is a prolonged increase in intrathoracic pressure. This increased pressure will necessarily reduce venous return such that these maneuvers are frequently associated with hypotension. Despite multiple studies, the mechanism of action of RMs is not clear. It seems that by increasing mean airway pressure throughout heterogeneous lung segments, areas of lung that have collapsed are opened. RMs improve ventilation and oxygenation by increasing the total lung capacity. Several types of RMs have been used. Amato et al.[10] used continuous positive airway pressure of 40 cm H_2O for 40 seconds followed by PEEP set 2 cm H_2O above the lower inflection point on the patient's pressure-volume curve (lower P_{flex}). This procedure proves to be cumbersome because it requires generation and interpretation of pressure-volume curves. Another method of lung recruitment named decremental PEEP adjustments was described by Hickling[11] and Girgis et al.[12] In this method, PEEP is decreased during low V_T ventilation to determine optimal lung compliance and the minimum PEEP level that optimizes oxygenation.

A provocative study by Gattinoni et al.[13] examined the relationship between the percentage of potentially recruitable lung and outcomes in 68 patients with ARDS. Interestingly, patients with a larger percentage of recruitable lung had inferior oxygenation and lung compliance, increased dead-space fraction, and significantly increased mortality. They explained their results by suggesting that patients with increased fractions of potentially recruitable lung likely had more severe underlying lung injury and therefore increased atelectasis at baseline.

Despite multiple clinical trials, there has not been a clear signal that RMs provide benefit. A systematic review by Fan et al.[14] that included 40 studies and 1185 patients showed that patients with ALI treated with RMs had transiently increased oxygenation with no significant increase in complications. Most common complications were transient, self-limited hypotension and oxygen desaturation. The authors concluded that RMs cannot be recommended or discouraged based on current evidence and should be considered for use on an individualized basis in patients with life-threatening hypoxemia.

PRONE POSITIONING

Prone positioning was first proposed by Bryan[15] in 1974 as physiotherapy for pediatric ICU patients. It has since gained popularity in adult patients because of its ability to improve oxygenation in patients with hypoxic respiratory failure. Pelosi et al.[16] in a comprehensive review of prone positioning ventilation in 2002 concluded that the beneficial physiologic effects of prone positioning could be attributed to recruitment of dorsal lung segments, improved $\dot{V}/\dot{Q}$ matching, and more homogeneous distribution of ventilation.

There are 2 methods of providing prone positioning ventilation. Traditionally, the patient is turned from supine to prone position on a standard ICU bed. This requires 3 to 6 specially trained people to ensure patient and provider safety. The other method is use of a proprietary bed that rotates the patient from the supine to the prone position. Regardless of the method used, patient safety concerns are the same. The most concerning side effects are airway compromise (loss of endotracheal tube or tracheostomy tube) by kinking or removal, loss of vascular access, pressure ulcers, and cardiac arrest.

Unfortunately, similar to positive pressure RMs, clear outcome benefit of prone positioning ventilation has not been demonstrated.[17–19] A recent meta-analysis including 4 trials and 1271 patients concluded that the odds ratio for ICU mortality was 0.97 (95% confidence interval [CI] 0.77–1.22) for prone versus supine ventilation in patients with hypoxemic respiratory failure.[20] The only faintly positive result was in the more severely ill group, in which prone positioning was favored (odds ratio 0.34; 95% CI 0.18–0.66). The caveat was that prone positioning was associated with a higher risk of pressure sores, and a trend for more complications related to the endotracheal tube. Alsaghir and Martin[21] also confirmed these results in a different meta-analysis. Most recently, in a study not included in the meta-analysis, Taccone et al.[22] were unable to find any benefit at all with prone positioning. Prone and supine patients had similar 28-day mortality rates. Outcomes were also similar for patients with moderate or severe hypoxemia. There were still higher complication rates related to prone positioning. When all of the available trials are included in the most recent meta-analysis by Sud et al.,[23] prone ventilation only reduced mortality in patients with Pao_2/Fio_2 <100 mm Hg (relative risk 0.84; 95% CI 0.74–0.96; $P = 0.01$), but the complications such as pressure ulcers, endotracheal tube obstruction, and chest tube dislodgement persisted. The authors concluded that given the associated risks, prone ventilation should not be routine for all patients, and only considered for the severely hypoxic.

At this time, there are no studies that specifically address the use of prone positioning in the setting of H1N1/influenza infection. However, given the profound hypoxemia that accompanies ARDS associated with influenza, RMs or prone positioning may be considered on an individual basis in patients with severe hypoxemia. Although mortality benefit has not been demonstrated, these techniques may serve as temporizing measures.

AIRWAY PRESSURE RELEASE VENTILATION

Airway pressure release ventilation (APRV; BiLevel in Europe) is a time-triggered, pressure-limited, time-cycled

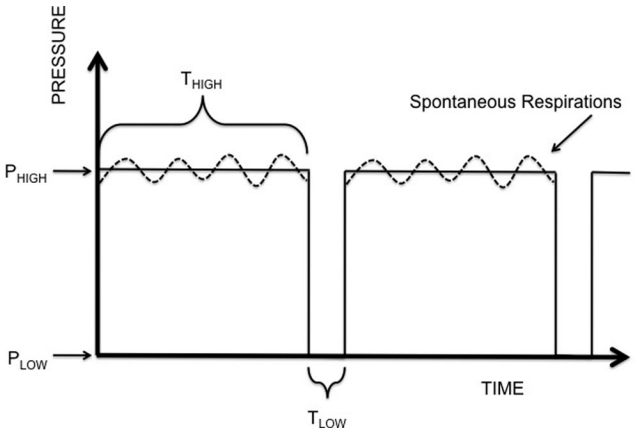

Figure 1. Pressure waveform describing airway pressure release ventilation. Two pressure levels are set (P_{high} and P_{low}). Note that inspiratory/expiratory time is prolonged and that the patient breathes spontaneously throughout the cycle.

mode of mechanical ventilatory support. In essence, a high level of continuous airway pressure (P_{high}) is applied for a specified time (T_{high}) with very brief periods (T_{low}) of release to a low level of continuous airway pressure (P_{low}). Figure 1 shows a pressure waveform describing APRV. APRV allows for a prolonged time at a higher mean airway pressure, thereby maintaining adequate lung volume and increasing alveolar recruitment to improve oxygenation. Depending on the severity of the lung injury, it may take up to 24 hours to see improvements in oxygenation. Some ventilation with elimination of carbon dioxide is achieved via the pressure release from P_{high} to P_{low}. Primary ventilation occurs with spontaneous breathing that is allowed at all pressure levels because of an active expiratory valve.

APRV probably has no advantages over conventional mechanical ventilation (CV) unless the patient is breathing spontaneously. In fact, in a heavily sedated and/or paralyzed patient, APRV is akin to time-cycled, pressure-limited, inverse ratio ventilation (pressure-controlled ventilation). With spontaneous ventilation, posterior- and caudal-dependent areas of atelectasis and lung consolidation improve when strong diaphragmatic excursion is allowed to occur from contraction. This would then improve ventilation and perfusion matching, resulting in improved oxygenation.[24–27] A spontaneously breathing patient would also have improved venous return with attenuation of a decrease in cardiac output caused by positive intrathoracic pressures from mechanical ventilation. A simultaneous decrease in right atrial pressure increases the inferior vena cava/right atrium gradient augmenting venous return. Experimental data have shown this to be the case despite the addition of high continuous positive airway pressure levels in spontaneously breathing patients. Adding pressure support to these breaths would more than likely eliminate these advantages.[27,28]

APRV can be initiated immediately after endotracheal intubation or as a rescue therapy after a trial of CV or HFOV. Initial P_{high} is normally the existing plateau pressure when transitioning from CV or mean airway pressure (P_{aw}) plus 2 to 4 cm H_2O when changing from HFOV. P_{low} is always set at 0 cm H_2O to maximize expiratory flow. T_{low} is usually set between 0.2 and 0.8 seconds. As patients are allowed to breathe spontaneously, pressure support can be added. This is not recommended because it negates the advantages of diaphragm movement on $\dot{V}/\dot{Q}$ matching explained previously.

After the initiation of APRV, there may need to be adjustments based on the degree of hypoxia and hypercapnia. To improve oxygenation, there needs to be an increase in P_{aw}. Increasing P_{low}, increasing P_{high}, increasing T_{high}, or decreasing T_{low} can achieve this. As patients are spontaneously breathing, to improve ventilation and CO_2 clearance, a provider can increase the P_{high} or increase the number of releases per minute. By increasing the pressure gradient between the P_{high} and P_{low}, V_T is augmented. Care should be taken not to increase the V_T beyond the recommended low V_T ventilation, if at all possible. Ventilation can also be improved by increasing the rate. However, by doing so, the amount of time spent at T_{high} decreases and there can be a consequent decrease in oxygenation.

Intuitively, APRV should require less sedation as ventilator synchrony is less of an issue. Oversedation is avoided and is considered detrimental, because spontaneous breaths are imperative for adequate ventilation and improved oxygenation. Indeed, early studies evaluating the utility of APRV showed that patients receiving APRV required significantly less sedation than those receiving traditional modes of mechanical ventilation.[29–36] However, these studies were small and some involved paralysis of the control patients. A recent study did show less usage of sedatives and analgesics in patients receiving APRV compared with patients receiving assist-control ventilation.[37] Interestingly, the majority of patients receiving APRV had primarily surgical/trauma diagnoses whereas the majority of patients receiving assist-control ventilation were medical patients. The medical patients did have a higher Acute Physiology and Chronic Health Evaluation (APACHE) II score.[37] A larger multicenter trial needs to be done to confirm these results.

Patients supported with APRV seem to require less sedation, which can lead to an increase in ventilator-free days and decrease in ICU stay. In 6 small crossover studies, APRV was shown to require lower inflation pressures and resulted in a higher Pao_2/Fio_2 ratio compared with CV.[29–34] In these studies, there was no apparent difference or there was an improvement in the Pao_2/Fio_2 ratio with APRV despite lower peak airway pressures. However, some of the studies have been questioned because of control groups that were not consistent with ARDSNet ventilator settings or involved heavy sedation and paralysis.[38] It should be noted that there are few studies available comparing APRV to standard CV. The small single-center studies that are available are all from the same group and have not shown any benefit with APRV over synchronized intermittent mandatory ventilation when focusing on ventilator-free days or mortality.

HIGH-FREQUENCY OSCILLATORY VENTILATION

The potential advantages of HFOV include: delivery of small V_T to limit alveolar overdistension, use of a higher mean airway pressure (mP_{aw}) to promote more alveolar recruitment, and maintenance of a constant mP_{aw} during

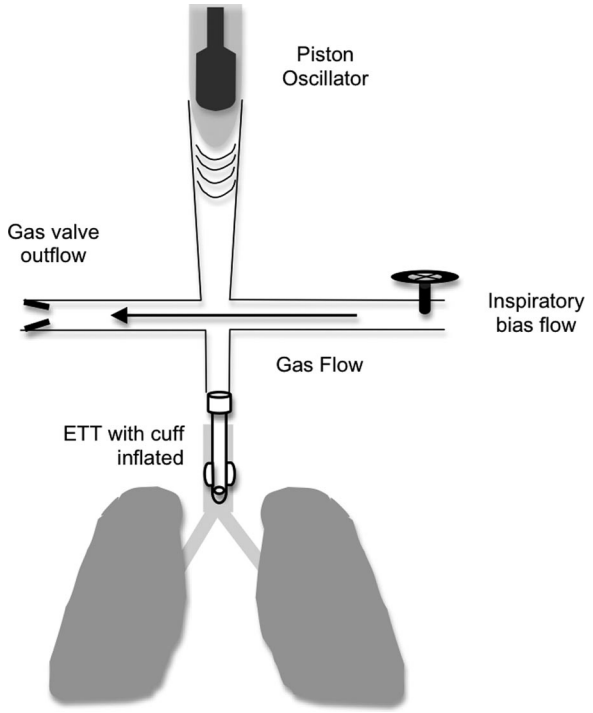

Figure 2. Schematic of high-frequency oscillatory ventilation. The piston oscillator provides active positive and negative pressure. Adjustment of the inspiratory bias flow and gas outflow valve determine mean airway pressure. ETT = endotracheal tube.

inspiration and expiration to prevent alveolar damage from recruitment and derecruitment (atelectrauma). The variables that are controlled directly on the SensorMedics 3100B ventilator (VIASYS Healthcare, Yorba Linda, CA) are frequency, amplitude of ventilation (power or ΔP), mP_{aw}, bias gas flow rate, percentage of inspiratory time, and FIO_2. Figure 2 is a schematic of HFOV.

A bias flow of humidified gas, along with a resistance valve in the circuit, is used to control the mP_{aw} within the circuit. The set power on the ventilator (ΔP) controls the distance that the piston pump moves. The oscillating piston pump then vibrates the gas at a set frequency, which achieves gas exchange by delivering very small VT. The return stroke of the piston during expiration creates a vacuum, leading to active expiration of gas, which is unique to HFOV compared with other modes of high-frequency ventilation. Problems with hypoxemia may be resolved by increasing FIO_2, performing RMs, or increasing mP_{aw} by increasing the bias flow, reducing the amount of gas vented out of the resistance valve, or increasing inspiratory time.

The exact timing (early versus late) and the severity level at which to transition to HFOV remain debatable. A consensus protocol for the initiation of HFOV and transition back to CV is lacking. A round table discussion was held in 2007[39] to recommend clinical thresholds for the institution of HFOV. Data extracted from randomized trials and cohort studies suggest that prolonged CV before transition to HFOV is not related to mortality.[40] Instead, the oxygenation index defined as (FIO_2 × mean airway pressure ×100)/PaO_2 is a more powerful predictor of mortality (relative risk 1.10; 95% CI 0.95–1.28).

Unfortunately, a large definitive clinical trial using HFOV in adults with ARDS is lacking and the literature in adults is mostly case series with only 2 randomized controlled trials reported. There are more extensive data in neonates, in whom numerous randomized clinical trials have been completed over the past 3 decades. However, data from neonatology cannot be extrapolated with confidence to adult medicine because of the pathologic difference in lung diseases (respiratory distress of a newborn versus ARDS) and different ventilator settings and respiratory care equipment.

Derdak et al.[41] conducted the largest multicenter randomized controlled trial that compared the safety and effectiveness of HFOV with CV in adults with ARDS. One hundred forty-eight patients with ARDS were randomized to CV versus HFOV. Although there was an initial improvement in PaO_2/FIO_2 with HFOV ($P = 0.008$), this difference did not persist beyond 24 hours. Mortality at 30 days was 37% in the HFOV group and 52% in the CV group ($P = 0.102$). The percentage of patients alive without mechanical ventilation at day 30 was 36% in the HFOV group and 31% in the CV groups ($P = 0.686$). There were no significant differences in hemodynamic variables, oxygenation failure, ventilation failure, barotrauma, or mucus plugging between the groups. The authors concluded that HFOV is a safe and effective ventilation mode for the treatment of ARDS. However, the improvement in oxygenation with HFOV was not sustained beyond 24 hours and improved oxygenation did not correlate with increased survival. Second, this trial was designed before the publication of the ARDSNet trial,[7] so the VT (10.6 mL/kg predicted body weight) and peak airway pressures (38 ± 9 cm H_2O) in the control group were higher than are currently considered the standard of care. The mortality trend in favor of HFOV may not be present in a more contemporary trial.

Bollen et al.[42] conducted a multicenter randomized controlled trial of HFOV versus CV in 61 adults with ARDS. A low VT strategy was used (average VT was 8 mL/kg predicted body weight). There were no significant differences in survival, therapy failure, or crossover rates between the 2 groups. In the HFOV group, the oxygenation index was significantly higher than in the CV group between the first and the second day, but the response of the oxygenation index to treatment did not predict survival versus death. The study was small and only had power to detect major differences in survival outcome, but there were no significant differences or even trends in mortality benefit when lower VT was used in the CV group.

The Canadian Critical Care Trials group is conducting one more trial. The OSCILLATE (The Oscillation for ARDS Treated Early) trial is undergoing pilot studies and hopes to answer the question of lung protection in patients with ARDS ventilated with HFOV or conventional low VT ventilation within 72 hours of intubation.† The enrollment of patients in the pilot study has been completed, but the data are currently under analysis.

†The Oscillation for ARDS Treated Early (OSCILLATE) Trial Pilot Study. Available at: http://clinicaltrials.gov/ct2/show/NCT00474656. Accessed March 7, 2010.

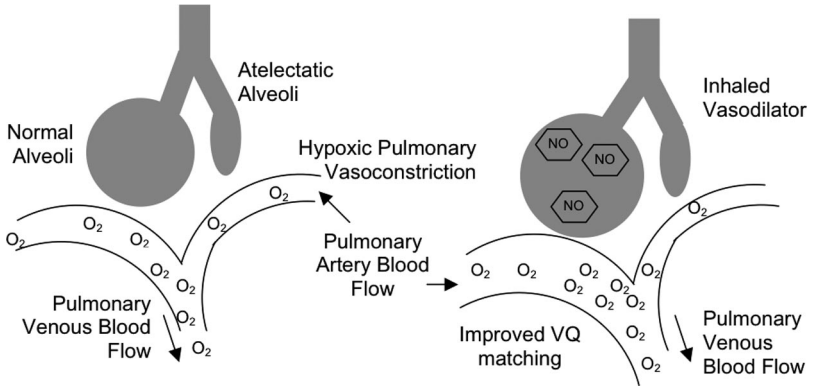

Figure 3. Delivery of inhaled nitric oxide (NO) to improve ventilation/perfusion ($\dot{V}/\dot{Q}$) matching. Note that vasodilation will occur selectively in areas where ventilation with NO occurs.

The data are inconclusive regarding the potential benefits of HFOV. Papazian et al.[44] compared in humans the physiologic and inflammatory effects of the combination of HFOV and prone positioning in patients with severe ARDS. With a prospective randomized design, 39 ARDS patients after 12 hours of CV received CV in prone position, or HFOV in supine or prone position. Interleukin-8 levels were significantly higher in the bronchoalveolar fluid of patients in both supine and prone HFOV groups versus CV. Whereas prone HFOV increased the Pao_2/Fio_2 ratio similarly to prone CV, prone HFOV was associated with higher bronchoalveolar fluid indices of inflammation. Our understanding of the effects of HFOV in humans is very rudimentary. The findings of Papazian et al. are concerning, and may explain why improvements in gas exchange with HFOV, such as prone ventilation, inhaled nitric oxide (iNO), and high PEEP,[19,45,46] have not always resulted in improved survival.

INHALED NITRIC OXIDE AND INHALED PROSTACYCLIN

The use of inhaled selective pulmonary vasodilators in the treatment of severe hypoxemia due to ARDS and ALI has been described in case reports and several clinical trials. Physiologically, this is an attractive treatment strategy. Although systemically administered pulmonary vasodilators carry the risk of reductions in systemic vascular resistance and resultant hypotension, inhalational delivery of short-acting substances has shown a high degree of pulmonary selectivity with minimal systemic effects. Figure 3 demonstrates the delivery of inhaled vasodilators. Theoretically, inhaled delivery of selective pulmonary vasodilators allows for recruitment of blood flow to ventilated lung units, sparing the nonventilated units, and thus improving $\dot{V}/\dot{Q}$ matching and hypoxemia. iNO and aerosolized prostacyclin are the 2 best studied selective pulmonary vasodilators that have been used in ARDS. Both have demonstrated efficacy at improving indices of oxygenation and reducing pulmonary vascular resistance. However, the effects on oxygenation seem to be short-lived and no study has been able to demonstrate an improvement in mortality or duration of mechanical ventilation.

Nitric oxide (NO) is a colorless, odorless gas, which mediates relaxation of vascular smooth muscle through activation of guanylyl cyclase and subsequent production of cyclic GMP.[47] Because of rapid inactivation by hemoglobin, NO has an exceedingly short half-life (seconds), which allows for selective pulmonary vasodilation when administered via inhalation without causing systemic vasodilation. Administration of iNO requires specialized equipment and its use can be quite costly. Because of its ability to promote pulmonary vasodilation, it has become an attractive treatment for both pulmonary hypertension and refractory hypoxemia. Disadvantages, although rare, include the accumulation of nitrogen dioxide and methemoglobinemia as well as in vitro evidence of deleterious effects on platelet aggregation and adhesion. At doses >40 ppm, methemoglobinemia can result from interactions between NO and oxyhemoglobin. Although rare, it is reasonable to consider periodic monitoring for methemoglobin. Effects on platelet aggregation and adhesion have also been described but have not been shown to be clinically relevant. Finally, nitrogen dioxide, formed when NO is administered with high levels of oxygen, and other reactive nitrogen species formed because of in vivo reactions of NO, may be cytotoxic and have proinflammatory effects.

A meta-analysis revealed that although iNO improved indices of oxygenation in the first 24 hours of ARDS treatment (with some studies showing improvement to 96 hours), there was also an increased risk of renal dysfunction and a trend toward increased mortality associated with the use of iNO.[48] These authors found that development of both methemoglobinemia and nitrogen dioxide was rare. They concluded that although iNO should not be routinely used for patients with ARDS and ALI, its use could still be considered in the setting of life-threatening hypoxemia.

Effects on oxygenation are modest but can be substantial in selected patients with severe hypoxemia. The dose range for iNO is 2 to 80 ppm and there can be significant interpatient variability.[47] The usual response is approximately a 20% increase in the Po_2 in blood with the most profound effect occurring at the lower end of the dose range (up to 20 ppm). It is recommended to start with a low initial dose (5 ppm) and titrate to a clinical end point periodically (every 30 minutes) up to 40 ppm. If no response occurs, iNO should be discontinued.‡ High doses (>40 ppm) have been associated with worsening oxygenation. This has been postulated to be caused by increased shunt precipitated by either "overflow" of NO into poorly ventilated lung units or by hemoglobin-bound NO species.

‡Available at: www.thoracic.org/clinical/critical-care/salvage-therapies-h1n1/pages/inhaled-vasodilators.php. Accessed March 7, 2010.

Caution must be used when withdrawing iNO because rebound pulmonary hypertension may result. It is recommended that a slow wean be performed with dose reductions made every 2 hours.

Prostacyclin, or epoprostenol, has been shown to have similar effects on the pulmonary vasculature as NO and has found extensive use in the treatment of pulmonary hypertension.[49,50] It has a very short half-life because of degradation to a much less potent metabolite. Although IV delivery, conventionally used in the treatment of pulmonary hypertension, would likely worsen shunting seen in ARDS/ALI, delivery by an inhaled route allows for the same, targeted delivery as with iNO.[51] Requiring no specialized delivery system, inhaled aerosolized prostacyclin (iAP) is also less costly than iNO. Platelet dysfunction is still a concern, but has not been shown to be of clinical significance.

There are only a few small studies evaluating iAP in patients with ARDS. All have shown efficacy at improving oxygenation and one sought to further characterize the dose-response relationship over the dose range of 10 to 50 ng/kg/min.[52] The authors were able to demonstrate improvements in indices of oxygenation at low doses with no demonstrable effects on pulmonary or systemic pressures. Although a clear dose-response relationship was demonstrated, they noted that the most profound effect was seen at initiation of the lowest dose (10 ng/kg/min) and postulated that the active metabolite of prostacyclin may be limiting the effects at high doses because of nonselective pulmonary vasodilation.

Delivery requires continuous nebulization of a reconstituted prostacyclin solution. Using a constant infusion rate of prostacyclin solution infused into an in-line nebulizer apparatus, the concentration of prostacyclin must be changed to alter the delivered dose.[52] Bronchospasm may result from aerosol delivery to the lung. Some authors have suggested starting at the highest dose and then downtitrating.‡ This will allow for the most rapid assessment of efficacy in a given patient, but caution must be used because the metabolite of prostacyclin does have vasodilatory properties and the lowest effective dose will minimize its accumulation. If no response occurs, therapy should be discontinued.

Although use of neither iNO nor iAP has reduced mortality in patients with ARDS/ALI, both can afford modest, short-term improvements in oxygenation, which can be significant in patients with severe, refractory hypoxemia. Either can be used to support patients until they recover, or alternative therapies can be used.

EXTRACORPOREAL LIFE SUPPORT

Extracorporeal life support has traditionally been used as cardiopulmonary bypass during cardiac surgery. With severe respiratory failure, it is logical to ask whether extracorporeal support could be used to support oxygenation and ventilation while the underlying infection and lung injury are treated. Anecdotally, extracorporeal membrane oxygenation (ECMO) is being used to treat patients with severe hypoxemia from H1N1 pneumonitis and has been used at our institution in 9 such patients. Given the extraordinary cost and resource utilization required for this rescue therapy, careful consideration of its efficacy must be considered.

The first randomized controlled trial comparing ECMO to conventional ventilator therapy in adults with acute respiratory failure was published by Zapol et al. in 1979.[53] Survival rates were poor in both arms (fewer than 10%) and the study failed to show any advantage of using ECMO. In 1994, Morris et al.[54] published the results of a second randomized controlled trial comparing extracorporeal carbon dioxide removal and low intermittent positive pressure ventilation versus pressure-controlled inverse ratio ventilation in adults with respiratory failure. This study also failed to show a significant difference in survival between the 2 groups (33% in the extracorporeal carbon dioxide removal group versus 42% in the pressure-controlled inverse ratio ventilation group). In a single-center study of patients with ARDS, Ullrich et al.[55] showed a surprising survival of 80% when a stepwise protocol including APRV, iNO, prone positioning, and ECMO was used.

Fueled by the potential benefits of ECMO demonstrated in several case series,[56–58] advocates of this therapy have sought a randomized controlled trial of modern ECMO techniques in adults with respiratory failure. The CESAR (Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial was a randomized controlled trial evaluating conventional ventilatory support versus a protocol that included ECMO for severe respiratory failure in adults. The primary outcome measure was death or severe disability at 6 months. One hundred eighty patients were enrolled and randomly allocated to consideration for treatment by ECMO versus conventional therapy. Consideration for ECMO was based on a Murray score of ≥ 3 (based on Pao_2/Fio_2 ratio, PEEP, lung compliance, chest radiograph appearance, and $Fio_2 = 1.0$) or uncompensated hypercapnia with a pH <7.2. Ninety patients were allocated to a highly experienced center for consideration of ECMO. If hemodynamically stable, they were placed on a standard protocol that included a low-pressure ventilation strategy, optimization of PEEP and Fio_2, diuresis, prone positioning, nutrition, and a target hematocrit. If the patient did not respond to the protocol within 12 hours, they received veno-venous ECMO. Of the 90 patients who were allocated for ECMO consideration, 3 died before transport, 2 died in transit, and 68 received ECMO. The other 17 patients received lung-protective ventilation per protocol as mentioned above. Overall, 63% of patients allocated to consideration for ECMO treatment survived to 6 months without disability compared with 47% allocated to conventional management. This translates into a 16% survival benefit without severe disability for patients in the group considered for ECMO. The authors of CESAR do acknowledge an important weakness: the lack of a standardized treatment protocol for the conventional group. Although a low-pressure and low-volume ventilation strategy was recommended, it was not insisted upon.[59] As an accompanying editorial states, the relative benefit reported in this study must be interpreted cautiously. The benefit may not be for ECMO but for referral to a center with expertise in providing specialized care.[59,60] All the referrals for ECMO were

Table 1. Summary of Randomized Controlled Trials for Rescue Therapies for Acute Hypoxemic Respiratory Failure

Rescue therapy	No. of patients	Oxygenation measurement	Mortality
Prone ventilation			
Gattinoni et al.,[19] 2001	304	Pao_2/Fio_2: higher in prone group	10-d mortality: ARR 0.039 (95% CI −0.055 to 0.133)
Guerin et al.,[62] 2004	791	Pao_2/Fio_2: higher in prone group	28-d mortality: ARR−0.01 (95% CI −0.074 to 0.055)
Voggenreiter et al.,[63] 2005	40	Pao_2/Fio_2: higher in prone group in first 4 d	90-d mortality: ARR 0.11 (95% CI −0.096 to 0.332)
Mancebo et al.,[64] 2006	136	Pao_2/Fio_2: higher in prone group starting at 4 h	ICU mortality: ARR 0.149 (95% CI −0.019 to 0.306)
Fernandez et al.,[65] 2008	42	Pao_2/Fio_2: higher in prone group after 6 h	60-d mortality: ARR 0.145 (95% CI −0.151 to 0.41)
Taccone et al.,[22] 2009	342	Pao_2/Fio_2: higher in prone group	28-d mortality: ARR 0.018 (95% CI −0.08 to 0.116)
APRV			
Varpula et al.,[66] 2004	58	Pao_2/Fio_2 ratio not statistically different after first 7 d	28-d mortality: ARR 0.012 (95% CI −0.184 to 0.212)
HFOV			
Derdak et al.,[41] 2002	148	Pao_2/Fio_2: improved in HFOV group for only 24 h	30-d mortality: ARR 0.147 (95% CI −0.012 to 0.297)
Bollen et al.,[42] 2005	61	Oxygenation index: higher in HFOV group between 1st and 2nd d	30-d mortality: ARR−0.099 (95% CI −0.32 to 0.148)
iNO			
Dellinger et al.,[67] 1998	177	Increase of Pao_2 ≥20% (response seen in 60% of patients)	28-d mortality: ARR 0.007 (95% CI −0.128 to 0.155)
Taylor et al.,[45] 2004	385	Increased Pao_2 (120 vs 100) seen in the first 24 h of therapy resolved by 48 h	28-d mortality: ARR−0.027 (95% CI −0.109 to 0.055)
Lundin et al.,[68] 1999	268	Increase of Pao_2 ≥20% (response seen in 67% of patients)	30-d mortality: ARR−0.039 (95% CI −0.179 to 0.104)
Inhaled prostacyclin			
Walmrath et al.,[50] 1996	16	Improved Pao_2/Fio_2 (114 to 135) and decreased PASP (35 to 31.9) similar to iNO	NA
ECLS			
Zapol et al.,[53] 1979	90		Long-term mortality: ARR 0.012 (95% CI −0.114 to 0.147)
Morris et al.,[54] 1994	40		30-d mortality: ARR−0.088 (95% CI −0.358 to 0.197)
Peek et al.,[59] 2009	180		6-mo mortality: ARR 0.133 (95% CI −0.011 to 0.27)

APRV = airway pressure release ventilation; ARR = absolute risk reduction; HFOV = high-frequency oscillatory ventilation; Fio_2 = fraction of inspired oxygen; PASP = pulmonary artery systolic pressure; CI = confidence interval; iNO = inhaled nitric oxide; ECLS = extracorporeal life support; ICU = intensive care unit; NA = not applicable.

made to a single center. The outcome may have been different if several ECMO centers had been used.[60]

Based on the above studies, including the most recent CESAR trial, a number of adult patients with refractory respiratory failure secondary to H1N1 have been treated with ECMO. The Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza investigators recently published their experience with the 2009 H1N1 season and the use of ECMO.[61] They collected data between June 1 and August 31, 2009 from all 187 ICUs in Australia and New Zealand. From this group, they identified 15 ICUs that provided ECMO. Two hundred one patients were treated with mechanical ventilation at the ECMO centers. Sixty-eight patients who failed conventional therapy received ECMO with the vast majority receiving veno-venous cannulation (93%) and the remainder veno-arterial (7%). Overall, in the patients who received ECMO, the median lowest Pao_2/Fio_2 ratio was 56, the lowest pH was 7.2, and the highest Fio_2 was 1.0. The patients had median modified ALI scores equal to 3.8. At the time of reporting, 71% of the patients who received ECMO had recovered and survived to ICU discharge. Forty-seven percent of the ECMO patients survived to hospital discharge. Overall, there was a 21% mortality rate in the ECMO group at the end of the study period.

CONCLUSIONS

Acute hypoxemia remains a major challenge in the management of critically ill patients. The H1N1 epidemic has renewed interest in salvage therapies for severe hypoxemic respiratory failure. It remains unclear at this time whether the data and practices learned from large studies in patients with ALI and ARDS can be translated to this unique patient population and applied to viral necrotizing pneumonia due to H1N1. Patients with H1N1 respiratory failure tend to be younger, have more severe hypoxemia, and have a more fulminant course. Although not specifically a therapy for hypoxemia, protective mechanical ventilation has the strongest evidence base, and should form the foundation for support of patients with ALI/ARDS. Therapies such as iNO and iAP, RMs, and HFOV have all shown the ability to improve oxygenation, but in the trials to date, have not shown a mortality benefit (Table 1). Given the substantial estimated cost of ECMO ($120,000 incremental cost using United Kingdom National Health Service estimate), extraordinary caution should be exercised before widespread

implementation. Conversely, the cost per quality-adjusted life year was between $7500 and $51,000, which is well within the range of cost effectiveness of other medical interventions. More problematic is the limited availability of ECMO, with only approximately 75 centers providing this therapy. At this time, the use of ECMO in H1N1 pneumonitis should be considered experimental. These studies do, however, remind us of the importance of receiving intensivist-driven critical care.

AUTHOR CONTRIBUTIONS

All authors helped to write the manuscript and approved the final manuscript.

REFERENCES

1. Salim A, Martin M. High-frequency percussive ventilation. Crit Care Med 2005;33:S241–5
2. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685–93
3. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, Sugerman DE, Druckenmiller JK, Ritger KA, Chugh R, Jasuja S, Deutscher M, Chen S, Walker JD, Duchin JS, Lett S, Soliva S, Wells EV, Swerdlow D, Uyeki TM, Fiore AE, Olsen SJ, Fry AM, Bridges CB, Finelli L. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009;361:1935–44
4. Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, Cretikos M, Davies AR, Finfer S, Harrigan PW, Hart GK, Howe B, Iredell JR, McArthur C, Mitchell I, Morrison S, Nichol AD, Paterson DL, Peake S, Richards B, Stephens D, Turner A, Yung M. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;361:1925–34
5. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, Stelfox T, Bagshaw S, Choong K, Lamontagne F, Turgeon AF, Lapinsky S, Ahern SP, Smith O, Siddiqui F, Jouvet P, Khwaja K, McIntyre L, Menon K, Hutchison J, Hornstein D, Joffe A, Lauzier F, Singh J, Karachi T, Wiebe K, Olafson K, Ramsey C, Sharma S, Dodek P, Meade M, Hall R, Fowler RA. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 2009;302:1872–9
6. Hemmila MR, Rowe SA, Boules TN, Miskulin J, McGillicuddy JW, Schuerer DJ, Haft JW, Swaniker F, Arbabi S, Hirschl RB, Bartlett RH. Extracorporeal life support for severe acute respiratory distress syndrome in adults. Ann Surg 2004;240:595–605
7. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8
8. Rothen HU, Sporre B, Englberg G, Wegenius G, Hedenstierna G. Re-expansion of atelectasis during general anaesthesia: a computed tomography study. Br J Anaesth 1993;71:788–95
9. Lichtwarck-Aschoff M, Nielsen JB, Sjostrand UH, Edgren EL. An experimental randomized study of five different ventilatory modes in a piglet model of severe respiratory distress. Intensive Care Med 1992;18:339–47
10. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, Kairalla RA, Deheinzelin D, Munoz C, Oliveira R, Takagaki TY, Carvalho CR. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347–54
11. Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. Am J Respir Crit Care Med 2001;163:69–78
12. Girgis K, Hamed H, Khater Y, Kacmarek RM. A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment. Respir Care 2006;51:1132–9
13. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354:1775–86
14. Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, Meade MO, Ferguson ND. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med 2008;178:1156–63
15. Bryan AC. Conference on the scientific basis of respiratory therapy: pulmonary physiotherapy in the pediatric age group—comments of a devil's advocate. Am Rev Respir Dis 1974;110:143–4
16. Pelosi P, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. Eur Respir J 2002;20:1017–28
17. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. Crit Care Med 1976;4:13–4
18. Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis 1977;115:559–66
19. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, Brazzi L, Latini R. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345:568–73
20. Kopterides P, Siempos II, Armaganidis A. Prone positioning in hypoxemic respiratory failure: meta-analysis of randomized controlled trials. J Crit Care 2009;24:89–100
21. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. Crit Care Med 2008;36:603–9
22. Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, Caspani L, Raimondi F, Bordone G, Iapichino G, Mancebo J, Guerin C, Ayzac L, Blanch L, Fumagalli R, Tognoni G, Gattinoni L. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 2009;302:1977–84
23. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guerin C, Mancebo J, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 2010;36:585–99
24. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J. Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1999;159:1241–8
25. Wrigge H, Zinserling J, Neumann P, Defosse J, Magnusson A, Putensen C, Hedenstierna G. Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. Anesthesiology 2003;99:376–84
26. Henzler D, Dembinski R, Bensberg R, Hochhausen N, Rossaint R, Kuhlen R. Ventilation with biphasic positive airway pressure in experimental lung injury. Influence of transpulmonary pressure on gas exchange and haemodynamics. Intensive Care Med 2004;30:935–43
27. Putensen C, Wrigge H. Clinical review: biphasic positive airway pressure and airway pressure release ventilation. Crit Care 2004;8:492–7
28. Hering R, Viehofer A, Zinserling J, Wrigge H, Kreyer S, Berg A, Minor T, Putensen C. Effects of spontaneous breathing during airway pressure release ventilation on intestinal blood flow in experimental lung injury. Anesthesiology 2003;99:1137–44
29. Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe acute respiratory failure. Chest 1991;100:460–3
30. Kaplan LJ, Bailey H, Formosa V. Airway pressure release ventilation increases cardiac performance in patients with acute lung injury/adult respiratory distress syndrome. Crit Care 2001;5:221–6

31. Rasanen J, Cane RD, Downs JB, Hurst JM, Jousela IT, Kirby RR, Rogove HJ, Stock MC. Airway pressure release ventilation during acute lung injury: a prospective multicenter trial. Crit Care Med 1991;19:1234–41
32. Schultz TR, Costarino AJA, Durning SM, Napoli LA, Schears G, Godinez RI, Priestley M, Dominguez T, Lin R, Helfaer M. Airway pressure release ventilation in pediatrics. Pediatr Crit Care Med 2001;2:243–6
33. Dart BWT, Maxwell RA, Richart CM, Brooks DK, Ciraulo DL, Barker DE, Burns RP. Preliminary experience with airway pressure release ventilation in a trauma/surgical intensive care unit. J Trauma 2005;59:71–6
34. Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA. Long-term effects of two different ventilatory modes on oxygenation in acute lung injury: comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. Am J Respir Crit Care Med 1994;149:1550–6
35. Putensen C, Zech S, Wrigge H, Zinserling J, Stuber F, Von Spiegel T, Mutz N. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001;164:43–9
36. Rathgeber J, Schorn B, Falk V, Kazmaier S, Spiegel T, Burchardi H. The influence of controlled mandatory ventilation (CMV), intermittent mandatory ventilation (IMV) and biphasic intermittent positive airway pressure (BIPAP) on duration of intubation and consumption of analgesics and sedatives: a prospective analysis in 596 patients following adult cardiac surgery. Eur J Anaesthesiol 1997;14:576–82
37. Fan E, Khatri P, Mendez-Telles P, Shanholtz C, Needham D. Sedation and analgesia usage with airway pressure release and assist-control ventilation for acute lung injury. Intensive Care Med 2008;23:376–83
38. Myers TR, MacIntyre NR. Respiratory controversies in the critical care setting: does airway pressure release ventilation offer important new advantages in mechanical ventilator support? Respir Care 2007;52:452–8
39. Fessler HE, Derdak S, Ferguson ND, Hager DN, Kacmarek RM, Thompson BT, Brower RG. A protocol for high-frequency oscillatory ventilation in adults: results from a roundtable discussion. Crit Care Med 2007;35:1649–54
40. Bollen CW, Uiterwaal CS, van Vught AJ. Systematic review of determinants of mortality in high frequency oscillatory ventilation in acute respiratory distress syndrome. Crit Care 2006;10:R34
41. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG, Carlin B, Lowson S, Granton J. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166:801–8
42. Bollen CW, van Well GT, Sherry T, Beale RJ, Shah S, Findlay G, Monchi M, Chiche JD, Weiler N, Uiterwaal CS, van Vught AJ. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. Crit Care 2005;9:R430–9
43. Deleted in proof.
44. Papazian L, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, Roch A, Forel JM, Bongrand P, Bregeon F, Sainty JM. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. Crit Care Med 2005;33:2162–71
45. Taylor RW, Zimmerman JL, Dellinger RP, Straube RC, Criner GJ, Davis K Jr, Kelly KM, Smith TC, Small RJ. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004;291:1603–9
46. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351:327–36
47. Griffiths MJ, Evans TW. Inhaled nitric oxide therapy in adults. N Engl J Med 2005;353:2683–95
48. Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ 2007;334:779
49. Haraldsson A, Kieler-Jensen N, Nathorst-Westfelt U, Bergh CH, Ricksten SE. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. Chest 1998;114:780–6
50. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. Am J Respir Crit Care Med 1996;153:991–6
51. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolised prostacyclin in adult respiratory distress syndrome. Lancet 1993;342:961–2
52. van Heerden PV, Barden A, Michalopoulos N, Bulsara MK, Roberts BL. Dose-response to inhaled aerosolized prostacyclin for hypoxemia due to ARDS. Chest 2000;117:819–27
53. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC II, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG Jr. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979;242:2193–6
54. Morris AH, Wallace CJ, Menlove RL, Clemmer TP, Orme JF Jr, Weaver LK, Dean NC, Thomas F, East TD, Pace NL. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295–305
55. Ullrich R, Lorber C, Roder G, Urak G, Faryniak B, Sladen RN, Germann P. Controlled airway pressure therapy, nitric oxide inhalation, prone position, and extracorporeal membrane oxygenation (ECMO) as components of an integrated approach to ARDS. Anesthesiology 1999;91:1577–86
56. Bartlett RH, Roloff DW, Custer JR, Younger JG, Hirschl RB. Extracorporeal life support: the University of Michigan experience. JAMA 2000;283:904–8
57. Nehra D, Goldstein AM, Doody DP, Ryan DP, Chang Y, Masiakos PT. Extracorporeal membrane oxygenation for nonneonatal acute respiratory failure: the Massachusetts General Hospital experience from 1990 to 2008. Arch Surg 2009;144:427–32
58. Conrad SA, Rycus PT, Dalton H. Extracorporeal Life Support Registry Report 2004. ASAIO J 2005;51:4–10
59. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009;374:1351–63
60. Zwischenberger JB, Lynch JE. Will CESAR answer the adult ECMO debate? Lancet 2009;374:1307–8
61. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettila V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M, Ziegenfuss M. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. JAMA 2009;302:1888–95
62. Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, Palmier B, Le QV, Sirodot M, Rosselli S, Cadiergue V, Sainty JM, Barbe P, Combourieu E, Debatty D, Rouffineau J, Ezingeard E, Millet O, Guelon D, Rodriguez L, Martin O, Renault A, Sibille JP, Kaidomar M. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 2004;292:2379–87
63. Voggenreiter G, Aufmkolk M, Stiletto RJ, Baacke MG, Waydhas C, Ose C, Bock E, Gotzen L, Obertacke U, Nast-Kolb D. Prone positioning improves oxygenation in post-traumatic lung injury: a prospective randomized trial. J Trauma 2005;59:333–41

64. Mancebo J, Fernandez R, Blanch L, Rialp G, Gordo F, Ferrer M, Rodriguez F, Garro P, Ricart P, Vallverdu I, Gich I, Castano J, Saura P, Dominguez G, Bonet A, Albert RK. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;173:1233–9
65. Fernandez R, Trenchs X, Klamburg J, Castedo J, Serrano JM, Besso G, Tirapu JP, Santos A, Mas A, Parraga M, Jubert P, Frutos F, Anon JM, Garcia M, Rodriguez F, Yebenes JC, Lopez MJ. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. Intensive Care Med 2008;34:1487–91
66. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesthesiol Scand 2004;48:722–31
67. Dellinger RP, Zimmerman JL, Taylor RW, Straube RC, Hauser DL, Criner GJ, Davis K Jr, Hyers TM, Papadakos P. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. Crit Care Med 1998;26:15–23
68. Lundin S, Mang H, Smithies M, Stenqvist O, Frostell C. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. Intensive Care Med 1999;25:911–9