Ventilator management for hypoxemic respiratory failure attributable to H1N1 novel swine origin influenza virus

Clare D. Ramsey, MD, MSc, FRCPC; Duane Funk, MD, FRCPC; Russell R. Miller III, MD, MPH; Anand Kumar, MD, FRCPC

Novel H1N1 swine origin influenza virus has led to a worldwide pandemic. During the pandemic, a significant number of patients became critically ill primarily because of respiratory failure. Most of these patients required intubation and mechanical ventilation and were treated with conventional modes of mechanical ventilation using a lung-protective strategy with low tidal volumes, plateau pressures <30 to 35 cm H2O, and optimal positive end-expiratory pressure. In some patients with persistent hypoxemia, alternative modes of ventilation, such as high-frequency oscillatory ventilation and airway pressure release ventilation, were used. We review the ventilatory management, recruitment maneuvers, prone positioning, and goals of ventilatory therapy for hypoxemic respiratory failure in general, as well as lessons learned in the management of H1N1-related respiratory failure.

**Key Words:** acute respiratory distress syndrome; H1N1; mechanical ventilation; influenza; swine flu; hypoxemic respiratory failure; low tidal volume ventilation; high-frequency oscillatory ventilation; noninvasive ventilation; acute lung injury

Novel H1N1 swine origin influenza virus was first reported in two children in California (1). After a large number of cases in Mexico, cases were reported in multiple countries worldwide (2). During this pandemic, significant numbers of patients with life-threatening disease required intensive care unit (ICU) admission primarily for hypoxemic respiratory failure.

Five types of respiratory presentations of H1N1 virus infection were seen: viral pneumonitis, exacerbations of asthma or chronic obstructive pulmonary disease, exacerbations of other underlying disease (i.e., congestive heart failure), secondary bacterial pneumonia, and croup/bronchiolitis in the pediatric population. The clinical presentation most frequently requiring ICU admission was viral pneumonitis. The majority of these patients presented with rapidly progressive hypoxemia and bilateral alveolar infiltrates on chest radiograph.

Most patients with hypoxemic respiratory failure required intubation and mechanical ventilation. Multiple modalities of mechanical ventilation were used in attempts to maintain adequate oxygenation (oxygen saturation >90%). This review focuses on the general ventilatory management of hypoxemic respiratory failure in the ICU, as well as lessons learned to date in the management of respiratory failure attributable to novel H1N1 swine origin influenza virus pneumonitis.

**Low Tidal Volume Ventilation**

During the mid to late 1990s, there was a paradigm shift in the way patients with acute respiratory distress syndrome (ARDS) were ventilated. Earlier it had been hypothesized that using large tidal volumes (~12 mL/kg and greater based on ideal body weight) would recruit atelectatic lung. Animal data seemed to indicate that large tidal volume (VT) ventilation created excessive alveolar distension and cyclic alveolar opening and collapse. This led to neutrophil activation and increased cytokine release, and thus greater ventilator-induced lung injury (VILI) (3, 4). Kolobow et al (5) showed that in addition to releasing inflammatory mediators, sheep ventilated at high VT vs. low VT died of respiratory failure and shock.

Amato et al (6) were the first to suggest that a different approach to ventilation might reduce the risk of VILI. Their ventilatory strategy attempted to limit the transpulmonary driving pressure diseased lungs are exposed to by decreasing VT to 6 mL/kg of actual body weight. To counteract the atelectasis that invariably occurs with a low VT strategy, positive end-expiratory pressure (PEEP) is titrated to a point just above the lower inflection point on the static pressure volume curve ("open-lung group"). PEEP was allowed to be as high as 24 cm H2O, and driving pressure (plateau pressure − PEEP) was allowed to be as high as <20 cm H2O. There was a significant improvement in pulmonary compliance, gas exchange, and weaning rate in the group ventilated with the open-lung approach compared to conventional ventilation (VT 12 mL/kg and minimum PEEP guided by the FIO2). There was no improvement in mortality rates, but the trial was small and thus not powered to detect such benefit.

The trial was continued to recruit a total of 53 patients, with 29 in the protective ventilation arm (6 mL/kg) and the
rest randomized to conventional ventilation (12 mL/kg) to examine mortality (7). A significant increase in the number of patients who were weaned (66% vs. 29%; \( p = .005 \)) and a decrease in clinically significant barotrauma (42% vs. 7%; \( p = .02 \)) was observed in the protective arm compared to the conventional ventilation arm. The decrease in barotrauma occurred despite aggressive levels of PEEP in the protective arm (mean PEEP of 16 cm H\(_2\)O in the first 2 days). Most importantly, the mortality rate was significantly reduced in the protective ventilation group (38% vs. 71%; \( p < .001 \)). However, this trial used multiple ventilatory strategies (low \( V_T \), open-lung ventilation, and recruitment maneuvers), so it is difficult to conclude which component had the largest impact on mortality.

Three other randomized, controlled trials failed to demonstrate a mortality benefit of the low \( V_T \) strategy in patients with ARDS or at risk for ARDS (8–10). There are several possible explanations for the contradictory results. In the negative studies, the differences in \( V_T \) between the intervention and control groups were much smaller (≈7 mL/kg vs. 10 mL/kg) compared to those in the study by Amato et al (6 mL/kg vs. 12 mL/kg). Additionally, plateau pressures (\( P_{PLAT} \)) were <35 cm H\(_2\)O in both arms of the negative trials, but not so in the Amato trial. Finally, the latter trial has been criticized for the high mortality rate in the control group (71%) compared to other ARDS trials.

The clinical equipoise resulting from these contradictory trials was resolved with the 2000 publication of the Acute Respiratory Management in ARDS (ARMA) trial from the ARDS Network (11). This multicenter trial enrolled 861 ARDS patients across the US and randomized them to either low \( V_T \) or traditional \( V_T \) ventilation. The low \( V_T \) group had a targeted \( V_T \) of 6 mL/kg of predicted body weight, with a goal \( P_{PLAT} \) <30 cm H\(_2\)O. The traditional ventilation group had a targeted \( V_T \) of 12 mL/kg predicted body weight and a goal \( P_{PLAT} <50 \) cm H\(_2\)O. The trial was stopped early because of a reduction in mortality in the low \( V_T \) group compared to traditional ventilation (39.8% vs. 31.0%; \( p = .007 \)). The low \( V_T \) arm also had a greater number of mechanical ventilation and nonpulmonary organ failure-free days. Again, this trial allowed the aggressive use of PEEP (up to 24 cm H\(_2\)O if \( FIO_2 \) was 1.0).

This led to a radical change in the ventilatory strategy of patients with ARDS and the recommendation that such patients be ventilated using the low \( V_T \) protocol from the ARMA study. That study, however, was not without detractors. The most common criticism was that the low \( V_T \) approach was not so much lung-protective because the high \( V_T \) strategy was injurious. Eichacker et al (12) suggested that the high \( V_T \) group did not represent the standard of care at the time of publication and thus was creating excess harm in the control group. The authors of the ARMA trial disputed these claims, noting that a survey from 1992 allowed physicians using a wide range of \( V_T \) in ARDS, including \( V_T \) as high as in the ARMA trial (13, 14). Currently, the low \( V_T \) strategy is recommended for the management of patients with ARDS.

Despite evidence supporting the use of low \( V_T \) in reducing mortality from ARDS, many clinicians have been slow in adopting this ventilatory strategy. Reasons for this are unclear, although evidence suggests that institutional and knowledge barriers contribute (15). Some physicians argue that using a \( V_T \) of 6 mL/kg has not been proven to be >8 mL/kg and therefore are reluctant to lower \( V_T \). In addition, concerns about patient comfort and the induction of hypercapnia and acidosis with this mode of ventilation have been raised. The low \( V_T \) strategy is generally well-tolerated but can result in higher levels of \( PaCO_2 \). This strategy, referred to as permissive hypercapnia, aims to limit end-inspiratory pressure and is generally tolerated until arterial pH declines to <7.15, at which time intravenous buffering agents such as NaHCO\(_3\) may be administered (16).

During the H1N1 pandemic, the low \( V_T \), open-lung approach was the ventilatory strategy chosen by many ICU physicians using conventional modes of mechanical ventilation to protect the lung from VILI and hopefully improve outcomes. Among our cohorts of patients from Canada and Utah, 68% to 80% were managed with pressure control or assist-control modes of ventilation with a targeted low \( V_T \) (<6 mL/kg) and \( P_{PLAT} <30 \) to 35 cm H\(_2\)O. Hypercapnia was generally not a major problem in this population but was permitted to reduce VILI. Some patients received a deviation from the targeted \( V_T \) (up to 8–9 mL/kg), primarily because of concerns of severe hypoxemia (because increased \( V_T \) increases mean airway pressure and therefore oxygenation) and, less frequently, acidemia. Barotrauma (pneumomediastinum or pneumothorax) was noted to occur in approximately 10% of patients in both cohorts. It was detected clinically or radiographically after the development of subcutaneous emphysema and was more common in patients in whom \( V_T \) was allowed to increase to improve acidemia or severe persistent hypoxemia. Very few cases of barotrauma contributed to hemodynamic compromise.

The Use of PEEP in ARDS: “The Open-Lung Approach”

In the early ARDS trials of low \( V_T \) ventilation, the use of PEEP was based on titrating end-expiratory pressure above the lower inflection point of the static pressure volume curve (6, 7). Low \( V_T \) ventilation invariably leads to areas of collapsed lung; therefore, PEEP is applied to counteract these effects by recruiting nonaerated lung. In the ARMA trial, PEEP was titrated based on \( FIO_2 \), and PEEP levels as high as 24 cm H\(_2\)O were used (11). These PEEP levels carry the potential for significant adverse hemodynamic effects, including decreased venous return and right ventricular dysfunction through increased right ventricular afterload.

The Assessment of Low Tidal Volume and Elevated End-expiratory Volume to Obviate Lung Injury (ALVEOLI) trial was a randomized controlled trial of 549 patients designed to determine whether higher or lower levels of PEEP would alter mortality in ARDS patients already receiving low \( V_T \) ventilation (\( V_T \) 6 mL/kg predicted body weight and \( P_{PLAT} <30 \) cm H\(_2\)O) (17). PEEP was titrated using a laddered approach determined by the patient’s \( FIO_2 \) and goal arterial oxygen saturation (\( SPO_2 \)) between 88% and 95%. The trial was stopped early on the basis of a prespecified futility rule. There was no difference between the higher (mean PEEP, 13.2 cm H\(_2\)O) and lower (mean PEEP, 8.3 cm H\(_2\)O) groups with respect to hospital mortality or number of patients breathing unassisted. A critique of the study was that the level of PEEP in the intervention group was altered after the first 171 patients, because the difference in PEEP between groups was less than that in the Amato (7) trial that showed a benefit with the open-lung approach. In addition, the \( PaCO_2/FIO_2 \) ratio was significantly lower and patients were significantly older at baseline in the
higher PEEP arm. The overall mortality rate in the study was 26.2%, which helped confirm the mortality benefit of the open-lung approach compared to controls in the initial ARDS Network trial.

Two larger trials, including a total of 1750 ARDS patients, compared higher vs. lower PEEP, along with low VT (target 6 mL/kg), and confirmed that high levels of PEEP did not result in improved mortality (18, 19). In the study by Meade et al (18), the open-lung/high PEEP arm maintained P\textsubscript{PLAT} <40 cm H\textsubscript{2}O and allowed recruitment maneuvers along with V\textsubscript{T} of 4 to 8 mL/kg, whereas the control arm maintained P\textsubscript{PLAT} <30 cm H\textsubscript{2}O, the same V\textsubscript{T}, and no recruitment maneuvers. PEEP was titrated based on F\textsubscript{io2} in both groups, but with higher PEEP (mean, 14.6 cm H\textsubscript{2}O) in the open-lung arm compared to 9.8 cm H\textsubscript{2}O in the control group. Lower rates of refractory hypoxemia and less use of rescue therapies (e.g., nitric oxide, high-frequency oscillatory ventilation [HFOV], and extracorporeal membrane oxygenation) occurred in the high PEEP arm. In the study by Mercat et al (19), PEEP was titrated to keep airway pressure as high as possible without P\textsubscript{PLAT} increasing >30 cm H\textsubscript{2}O; in the control group, PEEP was set at 5 to 9 cm H\textsubscript{2}O. More ventilator-free days, more days without organ failure, and better oxygenation were seen in the high PEEP group (19).

In aggregate, these studies would seem to suggest that higher levels of PEEP do not produce further benefit (with respect to mortality rates or ventilator-free days) when lower VT levels are used.

During the H1N1 pandemic, high levels of PEEP were often used to achieve adequate oxygenation (Sp\textsubscript{O2} >88–90%). Patients with bilateral alveolar infiltrates and severe hypoxemia were often PEEP refractory. In some, PEEP was increased to levels of 16 to 30 cm H\textsubscript{2}O with variable response in terms of oxygenation. It was also noted that once patients improved and the weaning process was started, oxygenation was sensitive to small decrements in PEEP. This process was often prolonged, and the best approach was that of watchful waiting with very small changes made daily to the ventilator settings. Various weaning approaches were performed; however, often an attempt was made to decrease PEEP <20 cm H\textsubscript{2}O before weaning F\textsubscript{io2} significantly.

HFOV

HFOV, an alternative mode of ventilation that fulfills the criteria as a lung-protective mode of ventilation, has been used successfully in neonatal and pediatric ICU for years. Studies in adults from the 1980s showed that high-frequency jet ventilation led to lower peak airway pressures and provided adequate gas exchange, but no improvement in other outcomes (20, 21). The use of HFOV re-emerged after studies showing the deleterious effects of higher V\textsubscript{T} ventilation. HFOV ventilates the lung with low V\textsubscript{T} (lower than anatomical dead space), which presumably avoids volutrauma and barotrauma. The higher mean airway pressure generated with HFOV translates into higher end-expiratory volume, which prevents atelectrauma (cyclic opening and collapsing of alveoli). Other potential benefits from HFOV include improved ventilation/perfusion matching and reduced barotrauma. Potential complications include retained secretions, mucous plugging, air trapping, and airway damage attributable to high gas velocities.

Animal studies have shown that HFOV improves oxygenation and lung compliance and reduces markers of inflammation in comparison to conventional low V\textsubscript{T} lung-protective ventilation (22). Most clinical studies to date are small, retrospective, and examined HFOV as a rescue therapy in patients with acute lung injury (ALI)/ARDS that did not respond to conventional mechanical ventilation. In the largest of these studies, HFOV was used primarily as a rescue therapy in patients requiring high F\textsubscript{io2} and/or high airway pressures, resulting in improvements in oxygenation and ventilation, but a high rate of pneumothorax. The mortality rate was high (62%), although patients had high Acute Physiology and Chronic Health Evaluation (APACHE) II scores and profound hypoxemia (average Pa\textsubscript{O2}/F\textsubscript{io2} = 91 ± 48 mm Hg). Independent predictors of mortality in this cohort were older age, higher APACHE II score, lower pH at initiation of HFOV, and a greater number of days on conventional mechanical ventilation before HFOV (23).

Similarly, prospective studies found improved oxygenation and Pa\textsubscript{CO2} with HFOV compared to conventional mechanical ventilation. In some studies the higher mean airway pressure with HFOV led to a significant decrease in cardiac output, although not below normal limits (24). In a smaller trial of 61 patients with ARDS randomized to conventional mechanical ventilation or HFOV, no mortality benefit was seen with HFOV; however, the trial was stopped early because of poor enrollment and significant crossover between treatment arms (25).

The Multicenter Oscillatory Ventilation for Acute Respiratory Distress Syndrome Trial (MOAT) study enrolled 148 ARDS patients and randomized them to HFOV vs. pressure-control ventilation. There was a trend toward lower mortality in the HFOV group; however, this was not significant and there was no difference in length of ventilation. A transient improvement in the Pa\textsubscript{O2}/F\textsubscript{io2} ratio was seen in the HFOV group, but this effect disappeared after 24 hrs (26). Future studies may be necessary to compare HFOV against lung-protective conventional ventilation strategy (V\textsubscript{T} 6 mL/kg and P\textsubscript{PLAT} <30 cm H\textsubscript{2}O) before HFOV can be recommended as a first-line therapy. The Oscillate pilot study, a randomized control trial of ARDS patients ventilated by HFOV or conventional open-lung ventilation to assess mortality, recently has been completed and may be better able to determine the role of HFOV in adult ARDS.

During the H1N1 epidemic, HFOV was used primarily as a rescue therapy when adequate oxygenation could not be achieved with conventional modes of ventilation. In the Canadian experience, HFOV was used in approximately 12% of patients (adults and children). Experience with HFOV in adults with H1N1 is limited by numbers, and its use was primarily dictated by the availability of the technology and center experience. Consideration may be given to using HFOV or other alternative modes of ventilation if patients have persistent hypoxemia (Sp\textsubscript{O2} <88–90%) despite conventional ventilation with low V\textsubscript{T} (4–8 mL/kg), adequate PEEP with an F\textsubscript{io2} ≥ 0.8, or P\textsubscript{PLAT} ≥ 35 cm H\textsubscript{2}O. There is currently no evidence of mortality benefit over conventional lung-protective ventilation. Therefore, if this mode of ventilation is being considered and is not available locally, the risk of transport in these critically ill patients must also be weighed.

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a mode of ventilation that applies continuous positive airway pressure to recruit alveoli and maintain lung vol-
ume with a time-cycled pressure release to a lower pressure for ventilation. APRV leads to lower peak and plateau pressures for a given $V_T$ than conventional pressure or volume-cycled ventilation (27). Theoretically, APRV should decrease the risk of alveolar overdistension because ventilation occurs with a decrease in airway pressure and lung volume. Spontaneous breathing is allowed and may recruit atelectic lung, particularly in dependent regions, without requiring higher airway pressures (28). During spontaneous breathing in APRV, the decrease in intrathoracic pressure should improve venous return, resulting in improved cardiac output and oxygen delivery (29).

A small number of clinical trials in ARDS or ALI patients found APRV improved oxygenation and allowed ventilation with lower peak airway pressures compared to conventional ventilation (28, 30, 31). In a multicenter, nonrandomized, crossover trial, patients with varying severity of ALI were placed on APRV and conventional ventilation sequentially for 30 mins. APRV was found to be a feasible alternative to conventional ventilation in terms of maintaining oxygenation and ventilation with a reduction in peak airway pressure; however, because of some concerns regarding the study design, further conclusions regarding the benefit of APRV cannot be made (32). The largest clinical trial to date randomized 58 patients with ALI or ARDS to APRV or synchronized intermittent ventilation with pressure support ventilation within 72 hrs of intubation. Inspiratory pressure was significantly lower in the APRV group, but there was no difference in hemodynamic parameters, $P_{aO_2}$/$P_{FIO_2}$, pH, or $P_{CO_2}$, or in 28-day or 1-yr mortality, or number of ventilator-free days (30). As with HFOV, current trials have not compared APRV to low $V_T$, open-lung protective ventilation.

Although APRV is theoretically an open-lung ventilatory strategy, there are potential concerns with APRV inducing VILI, particularly during spontaneous breathing, when the lung is subjected to negative pleural pressure and thus added stretch, which could induce VILI. Concern about atelectrauma dictates that time at lower pressure for ventilation is minimized. Because spontaneous breathing is encouraged with APRV, heavy sedation and paralysis are generally avoided. If the patient is unable to breathe spontaneously, then the benefits of APRV (lung recruitment, improved venous return, and avoidance of alveolar overdistension) over conventional ventilation may be lost. Finally, patients with significant obstructive lung disease likely will not tolerate APRV, because the time for exhalation is too short to empty their lungs and avoid hyperinflation.

The reported experience with APRV in H1N1-related hypoxemic respiratory failure is small. When used as a rescue therapy in a small number of patients, it was associated with an improvement in oxygenation, at least in the short term. Other modalities, such as nitric oxide, were often used in conjunction with alternative modes of ventilation, so the independent effect of each therapy was difficult to assess. Several patients with H1N1 infection presented with chronic obstructive pulmonary disease and asthma exacerbations. In these patients, APRV would not be the ideal mode of ventilation because of the need for rapid alveolar emptying, which is not present in these disorders. As with HFOV, APRV may be considered in patients with persistent hypoxemia ($Sp_{O_2} < 88–90\%$) despite conventional ventilation with low $V_T$ ($4–8 \text{ mL/kg}$), adequate PEEP with an $F_{IO_2} \geq 0.8$ or $P_{PLAT} \geq 35 \text{ cm H}_2\text{O}$, with the caveat that there is no proven mortality benefit.

**Noninvasive Ventilation**

Noninvasive ventilation (NIV) has been used as an alternative therapy for patients with acute respiratory failure with hopes of obviating intubation and mechanical ventilation. In this regard, NIV has shown a more consistent benefit in avoiding intubation among patients with hypercapnic as opposed to hypoxemic respiratory failure. The results of NIV in hypoxemic respiratory failure have been conflicting, and the etiology of hypoxemia appears to be an important determinant of its success. Patients with acute exacerbations of chronic obstructive pulmonary disease, acute cardiogenic pulmonary edema, or immunocompromise have been shown to benefit from NIV (33–35).

Confalonieri et al (36) studied patients with respiratory failure secondary to community-acquired pneumonia and found that only those with chronic obstructive pulmonary disease and hypercapnia on presentation avoided intubation, if treated with NIV compared to standard treatment. Similar results were seen in a smaller trial by Wysocki et al (37). The initial 1996 article by Meduri et al (38) reported NIV to be effective in hypoxemic respiratory failure, but there was no control group and the study was small. Subsequently, Ferrer et al (39) compared NIV to conventional ventilator oxygen delivery in patients with severe hypoxemic respiratory failure and found NIV decreased the need for intubation, as well as ICU and 90-day mortality. This benefit was observed in the subgroup of patients with severe community-acquired pneumonia, but not in those with ARDS/ALI, in which the intubation rates were high in both groups. Jolliet et al (40) found that despite initial improvement in oxygenation with NIV, a high rate of failure and subsequent intubation occurred in patients with community-acquired pneumonia and predominantly hypoxemic respiratory failure. A meta-analysis suggests that noninvasive positive pressure ventilation does not decrease the need for intubation, so there is not enough evidence to support its use in ARDS; however, the studies are heterogeneous and further investigation is likely warranted (41). Thus, the role of NIV in hypoxemic respiratory failure is less clear.

Whereas NIV may be considered as a mode of ventilation for hypoxemic respiratory failure, there are concerns about its usefulness in an infectious epidemic. NIV generates aerosols and there are no bacterial or viral filters on NIV (continuous positive airway pressure/bilevel positive airway pressure) machines, there is often a leak from the mask, and it often needs to be removed temporarily for nursing care. Thus, as with severe acute respiratory syndrome, concerns arose regarding the transmission of H1N1 with this mode of ventilation. NIV generates respiratory droplets and aerosols, which can reach a 0.5-m radius surrounding a patient receiving NIV (42). During the severe acute respiratory syndrome epidemic, NIV was shown to be a risk factor for transmission of disease to healthcare workers, although this was not statistically significant (43). Because of this potential risk, the use of noninvasive positive pressure ventilation was tailored during the severe acute respiratory syndrome epidemic.

In our initial experience, NIV was not successful in the majority of critically ill patients with hypoxemic respiratory failure from H1N1. In the Canadian experience, approximately 30% of patients were noninvasively ventilated on admission, but 85% of these patients required sub-
sequent intubation and invasive ventilation. Similarly in Utah, 33% of patients were initially treated with NIV (bilevel positive airway pressure) and approximately 85% subsequently required invasive ventilation. After this initial experience, patients were intubated earlier instead of waiting until their respiratory status deteriorated, and intubation was more complicated or uncontrolled. In several centers, NIV ventilation was used only for weaning after several weeks of invasive ventilation. In centers without negative pressure rooms, NIV was avoided because of concerns with aerosolization and disease transmission.

Reasons for failure of NIV in this population may be that patients present almost uniformly with hypoxemic respiratory failure and normal PaCO2. As mentioned previously, patients with purely hypoxemic respiratory failure are less likely to avoid intubation than those with hypercapnia with the use of NIV. In addition, improvement and resolution of H1N1 pneumonitis was generally slow, and thus NIV may be less useful. Longer use of NIV is associated with discomfort and facial skin breakdown. There are few patients with H1N1-related respiratory failure who seemed to benefit from this mode of ventilation alone, so it should be reserved for patients with milder disease whose anticipated need for ventilatory support is short and who can be closely monitored.

Recruitment Maneuvers

Recruitment maneuvers (RM) aim to open collapsed lung units and increase functional residual capacity by increasing transpulmonary pressure. To recruit lung, airway pressure must be greater than the critical or threshold opening pressure at end inspiration and must be kept above the closing pressure at end expiration (44). Studies have demonstrated improved oxygenation after RM, which can be sustained when adequate PEEP is applied after a maneuver (45, 46). Other studies either have shown no benefit in oxygenation or have found a variable response (47). These discrepancies may be attributable to the inherent heterogeneity in ARDS, partly related to the etiology (pulmonary vs. nonpulmonary) and the type and timing (early vs. late) of RM used (48, 49).

Amato et al (6) showed a survival benefit with their open-lung ventilation strategy that included RM, but the independent effects of RM could not be determined. The ALVEOLI trial attempted to study the independent effects of higher PEEP and RM (continuous positive airway pressure 35–40 cm H2O for 30 secs); however, no significant improvement in oxygenation was seen after the first 80 patients; therefore, this arm of the study was stopped (17). The study of Meade et al (47) included RM (continuous positive airway pressure 40 cm H2O for 4 secs) initially and after every ventilator disconnection as part of their open-lung approach to ventilation described previously. There was no mortality benefit in the open-lung group, but oxygenation improved and there was no difference in barotrauma between the open-lung group and controls (low VT and Pplat <30 cm H2O). No further studies have investigated RM and their effects on long-term outcomes, such as mortality rates, in patients with ARDS.

If RM are used, it is unclear which method should be used. A recent study found that sighs superimposed on lung-protective ventilation with optimal PEEP improved oxygenation and lung compliance more than optimal PEEP with one sustained inflation maneuver (continuous positive airway pressure 40 cm H2O for 30 secs) (46). The etiology of ARDS and the amount of recruitable lung also may determine the likelihood of response. Gattinoni et al (48) found that patients with a higher percentage of recruitable lung (based on chest computed tomography) had the best response to higher PEEP. A meta-analysis concluded that RM resulted in a significant improvement in oxygenation (Pao2/Fio2 increased from 139 to 251), and serious adverse events were infrequent. The most common adverse events were hypotension (12%) and desaturation (9%) (45).

Documented experience with the use of RM in patients with H1N1-related hypoxemic respiratory failure is limited, and thus no firm conclusions can be made. RM were used with variable short-term improvements in oxygenation. Because many of these patients were on high PEEP, whenever they were disconnected from the ventilator they had rapid desaturation, and thus RM were used to re-open collapsed alveoli. In patients already on high PEEP (>18 cm H2O), RM may have had less beneficial effect. The variability in response also may have been related to differences in the percentage of collapsed lung vs. ground-glass infiltrates on chest computed tomography.

Prone Position

Prone position has been utilized to improve oxygenation in patients with ARDS. Multiple physiologic mechanisms have been proposed to explain the improvement in oxygenation: alveolar recruitment, improvement in ventilation/perfusion matching from redistribution of ventilation to dorsal lung regions, elimination of the heart’s compressive effects on the lungs, and better drainage of respiratory secretions (50). Prone ventilation also is thought to reduce parenchymal lung stress (decrease transpulmonary pressure) and strain (Vt/end-expiratory lung volume), as shown in a small study in which prone ventilation reduced peak and plateau pressures, decreased lung elastance, improved oxygenation, and decreased dead space (51).

Although studies have shown a physiologic benefit with prone positioning, current literature has not demonstrated a mortality benefit (52–54). Approximately 70% of patients with ALI/ARDS improve their oxygenation in the prone position. The initial randomized control study by Gattinoni et al (52) randomized patients with ALI/ARDS to prone position for an average of 7 hrs daily for 10 days and found no significant difference in 10-day, ICU, or 6-mo mortality between groups despite a significant improvement in Pao2/Fio2 ratio in the prone group. The most common complication of the prone position was pressure sores, and the rate of endotracheal tube displacement or extubation was similar between both groups. In a post hoc analysis, subjects with more severe disease (Pao2/Fio2 ≤ 88, APACHE II score >49, and/or a high Vt >12 mL/kg of predicted body weight) had improved 10-day survival, but not thereafter. Caution must be used when interpreting these results, because they were post hoc findings with no correction for multiple comparisons. A subsequent retrospective review (55) of this trial found that responders to prone ventilation, defined by an improvement in CO2, had improved survival compared to nonresponders. The same was not true for responders and nonresponders based on Pao2. These results should be treated with caution because this also was a post hoc retrospective review and classification as a responder based on CO2 only required a ≥1-mm Hg decrease in CO2.

The largest and most recent study on prone positioning also failed to show a significant improvement in 28-day mor-
tality or length of mechanical ventilation (53). In the prone group, the incidence of ventilator-associated pneumonia was significantly lower and, as shown in other studies, PaO₂/FIO₂ was significantly higher. However, there were significantly more complications in the prone group, including endotracheal tube obstruction and pressure sores. Mancebo et al (56) randomized patients early in their ICU admission to a longer period in the prone position (an average of 17 hrs daily for 10 days) vs. supine ventilation. A 15% absolute reduction in ICU mortality was observed in the prone group, but this did not reach statistical significance. The study was underpowered and was stopped early because of poor enrollment.

Kopterides et al (57) conducted a meta-analysis of randomized control trials on prone ventilation in adults and found no difference in mortality. The pooled analysis for mortality in the most severely ill (defined as in the study by Gattinoni et al) favored prone position (odds ratio [OR], 0.34; 95% confidence interval [CI], 0.18–0.66), but almost all the data were from the Gattinoni study (52). In a second meta-analysis, which included a larger number of trials in both adults and children, the primary analysis for mortality was also negative, but there was a reduced risk of ventilator-associated pneumonia (relative risk, 0.81; 95% CI, 0.66–0.99) and a significant improvement in oxygenation (PaO₂/FIO₂ increased 23% to 34%) in the prone group (58). Prone positioning was found to be generally safe in centers familiar with it, but it was labor-intensive and did increase the risk of pressure ulcers.

Based on the current evidence, there is no mortality benefit to the prone position; however, it may improve oxygenation and therefore is an intervention that can be used in the setting of life-threatening hypoxemia in centers with experience with it. Again, as with RM, experience with prone ventilation in H1N1-related respiratory failure is limited and, in our experience, was tried in select patients with persistent hypoxemia (SpO₂ <88–90% despite FIO₂ >0.8). The potential short-term benefits must be weighed against the risks (accidental line and endotracheal tube removal, which could be catastrophic in these patients) and increased resources required. Patients who are hemodynamically unstable would be poor candidates because of the difficulty resuscitating a patient in the prone position. Because there is no mor-

tality effect in ARDS, prone positioning cannot be recommended routinely for patients with H1N1 but can be considered as a means to improve oxygenation when conventional open-lung ventilation is no longer meeting oxygenation goals.

Should We Lower Our Standards for Acceptable Oxygenation? Permissive Hypoxemia

One of the goals in management of ALI/ARDS is adequate oxygenation, which is generally defined as an oxygen saturation >90% or PaO₂ >60 mm Hg. In severe cases, this may be difficult to achieve when our other goals are to prevent VILI by limiting VT and P_plat. In these situations the question is often posed, “should we deviate from a low VT and/or low P_plat approach to achieve oxygenation goals, or should we lower the level considered as acceptable oxygenation?”

Several interventions in hypoxic respiratory failure (ALI/ARDS) have shown improvement in physiologic parameters (PaO₂/FIO₂, PaCO₂) yet have not translated into a survival benefit (e.g., prone position, HFOV, nitric oxide, and steroids). In addition, most patients with ARDS die of multisystem organ failure and not hypoxemia. Thus, perhaps oxygenation is not the best marker of irreversible lung damage and subsequent mortality.

Several studies have looked at long-term outcomes in survivors of ARDS. Hopkins et al (59) measured pulse oximetry in a prospective cohort of mechanically ventilated ARDS survivors to determine relationships between the duration and severity of mean SpO₂ <90% with neurocognitive outcomes. The length and time that the SpO₂ was <90% correlated significantly with neuropsychological sequelae at 1 yr after discharge ($r^2 = .31–.47$; all $p < .03$) (59). In a follow-up cohort study of ARDS patients followed-up for 2 yrs after hospital discharge, most had neurocognitive sequelae at hospital discharge, but this decreased significantly by 1 yr. Duration of hypoxemia, measured as time with SpO₂ <90%, was not significantly correlated with neurocognitive scores at 2-yr follow-up (60). This same group obtained computed tomography scans in a subset of ARDS survivors and found that there was significant brain atrophy compared to age- and sex-matched controls (61). The duration and severity of hypoxemia did not correlate with brain atrophy or ventricular enlargement. Because hypoxia is known to be associated with cerebral atrophy and diffuse neural loss, the authors concluded that the lack of association between computed tomography changes and degree of hypoxemia maybe attributable to the small study size or because computed tomography is not sensitive enough to pick up changes in the basal ganglia, hippocampus, and cerebellum, which are more susceptible to hypoxia. There was still no difference in functional outcomes compared in their earlier study (60).

Another study followed-up ARDS survivors from hospital discharge and >75% had no significant cognitive impairment at 6 yrs (62). Those with cognitive impairment primarily had problems with attention. Although the authors did not look specifically at severity or length of hypoxemia, they examined severity of illness (APACHE II), length of intubation, and use of extracorporeal membrane oxygenation, and they found these were not significant risk factors for cognitive impairment. Impaired attention has been related to psychological distress, whereas hypoxemia has been related primarily to impaired memory (63, 64). Thus, hypoxemia experienced by ARDS patients may not be the primary cause of their cognitive impairment after ICU discharge. Other factors contributing to cognitive impairment in patients with ARDS, apart from hypoxemia, are the use of sedatives, hypotension, glucose dysregulation, other organ failure, and the development and duration of delirium (65). Thus, altering from a protective ventilatory strategy to maintain SpO₂ >90% may not be necessary and could be deleterious (e.g., contribute to VILI). Perhaps we should focus on measures of tissue oxygenation, because the primary goal is to improve oxygen delivery defined by the following equation: oxygen delivery = cardiac output × arterial oxygen content [(1.34 × hemoglobin × SaO₂) + (0.003 × PaO₂)]. Higher arterial oxygen saturation does not necessarily equate with optimal tissue oxygenation (66). One way to minimize the need for oxygen delivery is by reducing oxygen consumption through reducing the work of breathing and aggressive treatment of fever (67).

Data in the literature are insufficient to support or refute the use of permissive hypoxemia. If lower oxygenation saturations are tolerated, then it is prudent to ensure adequate oxygen delivery at the
tissue level, possibly by close monitoring of mixed venous oxygen saturation and serum lactate levels.

Because of the degree of hypoxemia seen in many patients with H1N1 infection, lower SpO\textsubscript{2} (80–90%) measurements were occasionally tolerated if higher arterial saturations could not be achieved after maximizing FiO\textsubscript{2}, optimizing PEEP, altering ventilatory parameters to reduce patient–ventilator asynchrony, and reducing oxygen uptake by sedation and paralysis. Ensuring adequate oxygen delivery involves optimizing cardiac output and hemoglobin, in addition to SpO\textsubscript{2}, in these patients with persistent hypoxemia.

**Overall Recommendations for Patients With H1N1-Related Respiratory Failure**

A significant proportion of patients with hypoxemic respiratory failure were obese or pregnant. Early intubation and/or management in the ICU may be prudent, given the rapid progression of hypoxemia, to decrease the risk of intubation complications (e.g., inability to secure an airway) or profound hypoxemia and hemodynamic instability.

NIV was unsuccessful in most patients and led to invasive mechanical ventilation. Given the high failure rate and the duration of ventilatory support often required in patients with H1N1-related respiratory failure, routine use of NIV should be avoided.

Based on current evidence, patients should be managed with a low \( V_T \) (target \( V_T \), 6 mL/kg), open-lung strategy of ventilation, with PEEP titrated based on FiO\textsubscript{2} for goal \( P_{\text{PLAT}} \) <30 to 35 cm H\textsubscript{2}O and SpO\textsubscript{2} 88% to 90% per the ARDS Network protocol. PEEP levels higher than usually used may be necessary.

Alternative modes of ventilation, such as APRV and HFOV, were used in small numbers of patients with no obvious adverse effects. These modes, if available, may be considered in the setting of persistent hypoxemia (SpO\textsubscript{2} <88–90%, with high PEEP and FiO\textsubscript{2} >0.8) or when the goals of lung-protective ventilation cannot be met (\( P_{\text{PLAT}} \) =30–35; \( V_T \) >8 mL/kg), particularly in the setting of progressive patient decline.

Rescue therapies such as RM, neuromuscular blockade, and prone ventilation can be considered if oxygenation goals cannot be met (SpO\textsubscript{2} <88–90%, with high PEEP and FiO\textsubscript{2} >0.8) with the afore-mentioned ventilatory strategy, particularly in the setting of progressive patient decline. Consideration must be given to the risk and benefit of rescue therapies in each patient, along with center experience. Consider monitoring tissue oxygenation (mixed venous oxygenation and serum lactate) and ensuring adequate oxygen delivery instead of relying solely on SpO\textsubscript{2}.

**REFERENCES**

26. Bollen CW, van Well GT, Sherry T, et al: High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a ran-