RESCUE VENTILATION

SUMMARY

Death due to Acute Respiratory Distress Syndrome (ARDS) commonly results either from refractory hypoxemia (inadequate oxygenation despite elevated levels of inspired oxygen) or hypercarbia (inadequate ventilation due to high inspiratory pressures or risk of barotrauma/volutrauma). The goal of improving oxygenation and ventilation must always be balanced against the risk of further lung injury. Several different rescue therapies can be used when conventional mechanical ventilation fails to improve patient oxygenation. The optimal time to initiate these rescue therapies is within 96 hours of the onset of ARDS to maximize alveolar recruitment. These ventilator modes/therapies should be limited to patients with refractory hypoxemia and should not be considered first-line modes of mechanical ventilation.

RECOMMENDATIONS

- **Level 1**
  - Low tidal volumes (6-8 mL/kg ideal body weight) should be used to reduce mortality in ARDS.
- **Level 2**
  - Neuromuscular blockade should be considered in patients with early severe ARDS to improve 90-day survival and increase ventilator-free days.
  - Prone positioning, performed by an experienced multidisciplinary team, should be considered in patients with a PaO_2/FiO_2 ratio < 150 as it may reduce 28-day mortality.
- **Level 3**
  - Positive end-expiratory pressure (PEEP) is associated with improved survival among ARDS patients. Optimal PEEP may be determined using the patient's pressure–volume curve.
  - Pressure Control Ventilation (PCV) results in lower peak airway pressures and less barotrauma/ volutrauma compared to the same tidal volume delivered by Volume Control ventilation.
  - High-frequency oscillatory ventilation should not be used in patients with moderate to severe early ARDS as it has been shown to increase in-hospital mortality.
  - Recruitment maneuvers can transiently improve oxygenation for brief periods of time.
  - Inhaled prostacyclins may improve oxygenation and decrease pulmonary artery pressures.
  - Inhaled nitric oxide (iNO) may increase oxygenation but does not affect mortality; peak benefit occurs with an iNO dose of 20 ppm.
    - Clinically significant improvement in oxygenation following initiation of iNO should be demonstrated within the first hour of therapy to justify continued use.
  - Sildenafil may facilitate weaning from iNO.
  - Extracorporeal membrane oxygenation (ECMO) should be considered in patients who remain hypoxic despite maximal positive pressure ventilation.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Most critically ill patients can be successfully ventilated using conventional modes of mechanical ventilation such as synchronized intermittent mechanical ventilation (SIMV) and assist control ventilation (ACV), both examples of volume-controlled ventilation. A subset of such patients, however, will develop hypoxemia refractory to increases in inspired oxygen fraction (FiO_2) that can challenge the resuscitative skills of even the most experienced intensivist. This evidence-based medicine guideline presents a variety of "rescue" therapies, and the evidence supporting their use, that can be beneficial in both improving patient oxygenation / ventilation and survival from acute lung injury.

SIMPLE RESCUE THERAPIES

The "rescue therapies" described can be divided into "simple" and "advanced" therapies. The simple therapies are generally associated with less patient risk and cost and should be implemented before proceeding to the advanced therapies.

Positive End Expiratory Pressure (PEEP)

Increasing the level of PEEP is often the first consideration when faced with a patient with refractory hypoxemia. While higher PEEP settings may be required in patients with refractory hypoxemia, a PEEP greater than 20 cmH_2O is seldom required and may require the use of invasive hemodynamic monitoring to ensure appropriate intravascular volume status is maintained. In the decision-making for each patient, the potential benefit of high-level PEEP should be balanced against the risk of harm (ventilator-induced lung injury, barotrauma/volutrauma, hypotension). The benefit of PEEP depends upon the potential for recruitment of collapsed alveoli. If an increase in PEEP results in alveolar recruitment, intrapulmonary shunt is reduced and PaO_2 improves with the increased alveolar pressure redistributed among open and previously collapsed alveolar segments. If the recruitment potential is low, then an increase in PEEP will have a marginal effect on intrapulmonary shunt and PaO_2. Increased PEEP in such patients may over distend already-open alveoli, potentially causing ventilator-induced lung injury and increased dead space with redistribution of pulmonary blood flow to non-ventilated regions of the lungs. The potential for recruitment can frequently be identified by viewing the patient's pressure-volume loop. An inflection point that is shifted to the right usually indicates the need for increased PEEP. Alternatively, a brief 30-minute trial of increased PEEP can be utilized. If an increase in PEEP results in minimal improvement (or worsening) of PaO_2, an increase in dead space (increased $PaCO_2$) with stable minute ventilation, or worsening pulmonary compliance, alveolar recruitment is minimal. Conversely, if an increase in PEEP results in improved PaO_2, decreased $PaCO_2$, and improved compliance, recruitment is likely significant.

> Briel et al. performed a meta-analysis of data extracted from three trials comparing low vs. high PEEP in 2299 patients (1). Among patients without ARDS, mortality did not differ between patients receiving low vs. high PEEP [19% vs. 27%; Relative Risk (RR) 1.37; 95% confidence interval (CI) 0.98-1.92; p=0.07]. Among patients with ARDS, however, mortality was significantly lower among patients receiving higher PEEP (39% vs. 34%; RR 0.90; 95% CI 0.81-1.00; p=0.049). Rates of pneumothorax and vasopressor use were similar. The study concluded treatment with higher levels of PEEP was associated with improved survival among the subgroup of patients with ARDS.
>
> Halter et al. tested the hypothesis that collapsed alveoli opened by a recruitment maneuver would be unstable or recollapse without adequate PEEP (2). In a pig ARDS model, a microscope was utilized to view alveoli and determine their stability following a recruitment maneuver (peak pressure of 45 cmH_2O and PEEP of 35 cmH_2O for one minute). Standard modes of ventilation were used with PEEP of either 5 or 10 cmH_2O applied following the recruitment maneuver. Although both levels of PEEP demonstrated improved oxygenation, alveoli ventilated with PEEP of 10 cmH_2O were more stable and less likely to collapse. This suggests that recruitment followed by inadequate PEEP permits unstable alveoli to collapse and may result in ventilator-induced lung injury despite initially improved oxygenation.

Recruitment Maneuver

A recruitment maneuver is a transient increase in transpulmonary pressure intended to promote reopening of collapsed alveoli thereby improving gas exchange. Sustained inflation of the lungs using high inspiratory pressures of 30 to 50 cmH_2O is applied for durations of 20 to 40 seconds to promote alveolar recruitment.

A variation of this technique is the use of intermittent "sigh" breaths, using three consecutive sighs set at a pressure of 45 cmH_2O. An extended sigh has also been used in which there is a stepwise increase in PEEP and a decrease in tidal volume over two minutes to a CPAP level of 30 cmH_2O for 30 seconds. Another method applies an intermittent increase in PEEP based upon the inflection point of the patient's pressure-volume curve. Studies demonstrate that a recruitment maneuver can significantly improve oxygenation for four to six hours. However, it is unclear whether this is due to the recruitment maneuver, the PEEP titration strategy, or both. An improvement in oxygenation with a recruitment maneuver may indicate that the current level of PEEP is too low to prevent alveolar derecruitment. A recruitment maneuver may be of limited benefit when higher levels of PEEP are required. No prospective randomized controlled trials have demonstrated a survival benefit from the use of recruitment maneuvers.

Hodgson et al. evaluated recruitment maneuvers compared to standard care to improve oxygenation in adults with acute lung injury (3). Seven trials (1170 patients) met the inclusion criteria for this review. All trials included a recruitment maneuver as part of the treatment strategy. In two trials, the mode of ventilation in patients receiving a recruitment maneuver differed from the mode used in patients who did not receive a maneuver. The intervention group showed no significant difference in 28-day mortality (RR 0.73; 95% CI 0.46-1.17, p=0.2]. Similarly, there was no statistical difference in the risk of barotrauma (RR 0.50; 95% CI 0.07-3.52, p= 0.5) or difference in blood pressure (mean difference 0.9 mmHg, 95% CI -4.28-6.08, p=0.73). Recruitment maneuvers significantly increased oxygenation above baseline for a brief period in four of the five studies that measured oxygenation.

Arnal et al. performed a prospective study of recruitment maneuvers in 50 sedated patients within the first 24 hours of meeting ARDS criteria (4). A 40 cmH_2O sustained inflation recruitment maneuver was performed for 30 seconds. Invasive arterial pressures, heart rate, and SpO_2 were measured at 10 second intervals during the recruitment maneuver. The volume recruited during the recruitment maneuver and time required to achieve the increase were measured. The average volume increase and time were 210 ± 198 mL and 2.3 ± 1.3 seconds respectively. Heart rate, diastolic arterial pressure, and SpO_2 did not change during or after the recruitment maneuver. Systolic and mean arterial pressures were maintained at 10 seconds, decreased significantly at both 20 and 30 seconds during the recruitment maneuver, and recovered to baseline within 30 seconds after the end of the recruitment maneuver ($p<0.01$). The authors concluded that in early-onset ARDS patients, most of the recruitment occurs during the first 10 seconds of a sustained inflation recruitment maneuver.

Pelosi et al. evaluated ten patients with ARDS treated with two hours of a lung protective strategy, one hour of lung protective strategy with three consecutive sighs/minute at a plateau pressure of 45 cm H_2O, followed by one hour of lung protective strategy (5). Total minute ventilation, PEEP (14±2 cm H_2O), inspiratory oxygen fraction, and mean airway pressure were kept constant. After one hour of sigh breaths, PaO_2 increased from 93±19 to 138±24 mmHg ($p<0.01$), venous admixture decreased from 38±12 to 28±14% ($p<0.01$), and $PaCO_2$ deceased from 53±19 to 49±18 mmHg ($p<0.05$). End-expiratory lung volume increased from 1.5±0.6 to 1.9±0.7 L ($p<0.01$) and was significantly correlated with both oxygenation ($r=0.82$, $p<0.01$) and lung elastance ($r=0.76$, $p<0.01$) improvement. Sigh was more effective in ARDS due to extrapulmonary causes than in ARDS due to pulmonary etiology. After one hour of sigh interruption, all the physiologic variables returned to baseline. The derecruitment was correlated with $PaCO_2$ ($r=0.86$, $p<0.01$). The authors concluded that 1) lung protective strategies alone at the PEEP level used in this study may not provide full lung recruitment and best oxygenation and 2) application of sighs during a lung protective strategy may improve alveolar recruitment and oxygenation.

Lapinsky et al. applied a sustained inflation maneuver of 45 cmH_2O or the peak pressure at a tidal volume of 12 mL/kg, whichever was lower, for a period of 20 seconds (6). An improvement in oxygen saturation was noted in all patients; in 10 out of 14 patients, this was sustained for up to four hours. No significant adverse effects were noted.

Lim et al. used an extended sigh as a recruitment maneuver (7). This involved gradually reducing tidal volume from 8 to 2 mL/kg and increasing the PEEP from 10 to 25 cmH_2O in a stepwise manner, each step lasting 30 seconds. When a tidal volume of 2 mL/kg and a PEEP of 25 cmH_2O were reached, a continuous positive airway pressure (CPAP) level of 30 cmH_2O was applied for 30 seconds following

which a reverse sequence was applied till the baseline settings were reached. PaO_2 increased significantly following this recruitment maneuver and the increase was more pronounced for patients in the supine vs. prone position. The authors recommended that sufficient PEEP is necessary in such patients as a decruitment strategy and that recruitment maneuvers may obviate the need for prone positioning in ARDS patients (see "Prone Positioning" below).

Constantin et al. compared two different recruitment maneuvers: a) CPAP of 40 cmH_2O for 40 seconds without tidal ventilation and b) increasing PEEP to 10 cmH_2O above the lower inflection point on the patient's pressure-volume curve for a period of 15 minutes while on volume-controlled ventilation (8). Both maneuvers similarly improved oxygenation at 5 and 60 minutes. However, only the inflection point-based maneuver was associated with an increase in recruited volume at both 5 and 60 minutes. Systolic pressure dropped below 70 mmHg during the CPAP maneuver on two occasions resulting in interruption of the recruitment maneuver while there was no significant blood pressure drop with the inflection point-based maneuver.

Low Tidal Volume Ventilation

The 2000 Acute Respiratory Distress Syndrome Network (ARDSNet) trial was conducted to compare a lung-protective strategy using lower tidal volumes of 6 mL/kg (goal plateau pressure <30 cmH_2O) versus "traditional" tidal volumes of 12 mL/kg (goal plateau pressure <50 cmH_2O) (9). The trial was stopped prematurely when the low tidal volume arm demonstrated a significant decrease in mortality (31% vs. 40%) and more ventilator-free days (12 vs. 10 days) compared to the traditional tidal volume arm. The use of 12 mL/kg has been criticized as being higher than the actual "traditional" standard of care at the time. The original ARDSNET protocol oversimplified lung protection and has subsequently been re-evaluated. Nevertheless, despite the trial's controversies, the use of low tidal volume ventilation (6-8 mL/kg) is now considered standard in patients with acute lung injury. The use of elevated levels of PEEP, recruitment maneuvers, and other rescue strategies (not addressed in the ARDSNET protocol) have since been identified as essential elements of any oxygenation improvement strategy.

Meade et al. performed a randomized controlled trial in 30 intensive care units in Canada, Australia, and Saudi Arabia (10). Nine hundred eighty-three consecutive patients with acute lung injury and a PaO_2/FiO_2 ratio of ≤ 250 were studied. The control strategy included target tidal volumes of 6 mL/kg of predicted body weight, plateau airway pressures ≤ 30 cmH_2O, and conventional levels of PEEP (n = 508). The experimental strategy included target tidal volumes of 6 mL/kg of predicted body weight, plateau pressures ≤ 40 cmH_2O, recruitment maneuvers, and higher PEEP levels (n = 475). The primary outcome measure was all-cause hospital mortality. Eighty-five percent of patients met criteria for ARDS at enrollment. Tidal volumes were similar in both arms. Mean PEEP during the first 72 hours was 9.8 ± 2.7 cmH_2O in the control arm vs. 14.6 ± 3.4 cmH_2O in the experimental arm ($p<0.001$). All-cause hospital mortality rates were 40% vs. 36% respectively (RR 0.90; 95% CI 0.77-1.05; p=0.19). Barotrauma rates were 11% vs. 9% (RR 1.21; 95% CI, 0.83-1.75; p=0.33). The experimental group had lower rates of refractory hypoxemia (10% vs. 5%; RR 0.54; 95% CI 0.34-0.86; p=0.01), death with refractory hypoxemia (9% vs.4%; RR 0.56; 95% CI, 0.34-0.93; p=0.03), and need for rescue therapies (9% vs. 5%; RR 0.61; 95% CI, 0.38-0.99; p=0.045) compared to the ARDSNET protocol strategy. The experimental strategy resulted in no significant difference in all-cause hospital mortality or barotrauma compared with the original ARDSNET strategy, but significantly improved the incidence of death due to refractory hypoxemia by using rescue therapies.

Pressure-Controlled Ventilation

Pressure control ventilation (PCV) is a mode of ventilation that delivers the patient's breath at a set pressure instead of by a preset tidal volume (as in volume control modes such as SIMV or ACV) (Figure 1). Once the preset inspiratory pressure is reached, the ventilator enters the exhalation phase. Unlike volume-controlled ventilation, where a set tidal volume results in a variable peak inspiratory pressure based upon the patient's pulmonary compliance, the peak inspiratory pressure of pressure-controlled ventilation results in a variable tidal volume based upon lung compliance and airway resistance. An increase in lung compliance will cause the size of the breath delivered to increase, and a decrease in lung compliance will cause the

tidal volume to decrease. The length of a breath is controlled by a set inspiratory time instead of by the peak flow. With PCV, the peak flow is variable so that the lowest peak inspiratory pressure is achieved for each breath. As a result, the incidence of barotrauma is lessened. PCV is most commonly used in patients with ARDS whose lung compliance is decreased, causing the lungs to become stiff and hard to ventilate. PCV is thus a commonly utilized rescue therapy in acute lung injury. With PCV, you can set an acceptable peak pressure and know that the patient will not exceed this pressure level. The downside is that the patient's tidal volume may drop if lung compliance worsens resulting in decreased ability to oxygenate and ventilate the patient unless the peak inspiratory pressure limit is increased.

Kallet et al. reviewed the effects of pressure-control vs. volume-control ventilation on patient work of breathing in acute lung injury and ARDS (11). Work of breathing was measured in a prospective, randomized cross-over study of 18 mechanically ventilated adult patients with acute lung injury or ARDS. At comparable levels of respiratory drive and minute ventilation, patient work of breathing was significantly lower with PCV than with volume-control ventilation ($p< 0.05$).

Rappaport et al. completed a randomized, prospective trial of 27 patients treated for severe acute hypoxic respiratory failure ($PaO2/FiO_2$ ratio of < 150) (12). Patients were ventilated using either PCV or volume-control ventilation. Despite similar APACHE II scores and PaO_2/FiO_2 ratios, peak airway pressure was consistently lower in patients randomized to PCV ($p=0.05$). PCV was also associated with a more rapid increase in static pulmonary compliance ($p=0.05$). There was a trend toward more rapid normalization of $PaCO_2$ in patients treated with pressure-limited ventilation. PCV patients who survived their illness and were extubated required fewer days of mechanical ventilation ($p=0.05$). The authors concluded that PCV is associated with lower peak airway pressures and more rapid improvement in static pulmonary compliance than volume-controlled ventilation.

Permissive Hypercapnea

Treatment of refractory hypoxemia and hypercapnia not infrequently results in worsening of one parameter in favor of the other. Attempts to improve oxygenation through increased airway pressures may result in hypoventilation and hypercapnia. Of the two, adequate oxygenation is most important to preserve oxygen delivery at the end-organ level and avoid worsening organ dysfunction and failure. Allowing a patient's pH to fall to >7.20 and $PaCO_2$ to increase up to 70 mmHg is generally well-tolerated and is known as "permissive hypercapnia". It is useful where increasing a patient's ventilatory support settings to normalize $PaCO_2$ to a "normal" range may be detrimental and unnecessary to the patient. Permissive hypercapnia is generally contraindicated in patients with cerebral edema, mass lesions or seizures, active coronary artery disease, arrhythmias, hypovolemia, and gastrointestinal bleeding among others. The potential risks of hypercapnia must be weighed against the relative risks of ARDS vs. ventilator-induced lung injury.

ADVANCED RESCUE THERAPIES

When the simple rescue therapies described above do not sufficiently improve a patient's oxygenation, a variety of more advanced rescue therapies remain available. These are more labor-intensive and associated with increased patient risk but may become necessary to restore adequate systemic oxygenation and ventilation.

Neuromuscular Blocking Agents (NMBA)

Breath stacking and patient-ventilator dyssynchrony both contribute to ventilator-induced lung injury. Clinicians commonly rely on NMBAs in the management of ARDS to prevent patient-ventilator dyssynchrony, to minimize work of breathing, and to improve oxygenation.

The 2010 ARDS (ACURASYS) trial (sometimes referred to as the Papazian trial) randomized 340 intubated patients with early severe ARDS to cisatracurium-induced paralysis or placebo for 48 hours (13). Cisatracurium use was associated with a 9% absolute reduction in mortality at discharge or 90 days (32% vs. 41%; $p=0.04$). Paralysis was also associated with a reduction in barotrauma (5% vs. 12%; $p=0.03$), pneumothorax (4% vs. 12%; $p=0.01$), days out of the ICU (48 vs. 40 days; $p=0.03$), and days not on the ventilator (53% vs. 45%; $p=0.03$).

Alhazzani et al. conducted a systematic meta-analysis for randomized trials investigating survival effects of NBMAs in adults with ARDS (14). Three trials (431 patients; 20 centers) met inclusion criteria for this review all of which assessed 48-hour infusions of cisatracurium besylate. Short-term infusion of cisatracurium was associated with lower hospital mortality (p=0.005). Neuromuscular blockade was also associated with lower risk of barotrauma (p=0.02) but had no effect on the duration of mechanical ventilation among survivors (p= 0.93) or the risk of ICU-acquired weakness (p=0.57). Their conclusion was that short-term infusion of cisatracurium besylate reduces hospital mortality and barotrauma and does not appear to increase ICU-acquired weakness for critically ill adults with ARDS.

Inverse Ratio Ventilation

Inverse ratio ventilation (IRV) is a modification of traditional modes of ventilation in which the normal inspiration-expiration cycle is "reversed" to maintain a greater inspiratory (I) than expiratory (E) time. This is used to improve oxygenation by recruiting collapsed alveoli through increased mean airway pressure. While a normal I:E ratio is 1:2, 1:3, 1:4, IRV reverses this ratio to 2:1, 3:1, 4:1, etc… IRV is most commonly utilized as a modification of PCV known as *Pressure Control Inverse Ratio Ventilation (PC-IRV)*. In addition to setting an inflation pressure and frequency, the inspiratory or "I-time" is increased such that it exceeds the expiratory or "E-time". PC-IRV is associated with a higher mean airway pressure (Paw) than standard modes of ventilation and Paw becomes the key determinant of gas exchange. As reversed I:E ratios are not comfortable, deep sedation and pharmacologic paralysis using NBMAs is necessary to prevent patient-ventilator dys-synchrony. Prolonged sedation and neuromuscular blockade may contribute to patient confusion, inability to clear secretions, increased muscle catabolism and inability to assess neurologic status.

Zavala et al. compared IRV vs. controlled mechanical ventilation (CMV with and without PEEP in eight patients with ARDS (15). Respiratory blood gases, inert gases, lung mechanics, and hemodynamics were measured 30 minutes after the onset of each ventilatory mode. PaO_2 increased 13 mmHg with CMV+PEEP and 10 mmHg with volume-control IRV compared to CMV alone ($p<0.05$). In contrast, PC-IRV did not affect PaO_2, but decreased $PaCO_2$ by 7 mmHg due to a decrease in dead space ($p<0.05$). The authors concluded that short-term PC-IRV improved carbon dioxide clearance.

Papadakos et al. retrospectively analyzed 30 surgical patients with ARDS treated with PC-IRV (16). Mortality was 10%. PaO_2 improved from 41 ± 12 mmHg to 47 ± 14 mmHg, while $PaCO_2$ decreased from 38 ± 8 mmHg to 31 ± 6 mmHg. They concluded that PC-IRV may be beneficial to surgical patients with ARDS.

Inhaled Prostacyclins

Prostacyclins are naturally occurring prostanoids that are endogenously produced as metabolites of arachidonic acid in the vascular endothelium. Inhalation of prostacyclins produces selective pulmonary vasodilation which can improve oxygenation in some patients. However, the vast majority of the relevant research in adults is from studies that address pulmonary hypertension and or right heart failure, rather than ARDS. Although high-level evidence is lacking to support its use, aerosolized prostacyclin offers a lower-cost alternative to inhaled nitric oxide (iNO) as a pulmonary vasodilator. Aerosolized epsoprotenol has been demonstrated to be an effective alternative to iNO as a pulmonary vasodilator in the acute care setting. Because of its short half-life, epoprostenol is continuously inhaled at 10 to 50 ng/kg/min.

Iloprost is the first inhaled prostaglandin to be approved by the US Food and Drug Administration for the treatment of pulmonary arterial hypertension. Iloprost is a stable prostaglandin with a half-life of 20 to 30 minutes and duration of effect of up to 120 minutes. Inhaled treprostinil and iloprost have been shown to produce comparable decreases in pulmonary vascular resistance, but inhaled treprostinil has not been evaluated in critically ill patients. Aerosolized alprostadil improves oxygenation in infants with hypoxic respiratory failure. The dose of inhaled prostacyclin may vary based upon the nebulizer system utilized. The type of nebulizer used may also affect the tidal volume delivered. Continuous nebulization of prostacyclin may occlude a ventilator's expiratory filters and cause malfunction of the expiratory valves.

Fuller et al. aimed to determine whether inhaled prostaglandins are associated with improvement in pulmonary physiology or mortality in patients with ARDS (17). They reviewed 25 studies (including two RCTs) published over 21 years. One RCT showed no difference in PaO_2/FiO_2 ratio when comparing inhaled alprostadil to placebo (p=0.21). Meta-analysis of the remaining studies demonstrated that inhaled prostaglandins were associated with improvement in PaO_2/FiO_2 ratio (16 studies; 39% higher; 95% CI 27%-51%), PaO_2 (eight studies; 21% higher; 95% CI 12%-31%), and a decrease in pulmonary artery pressure (-5 mmHg; 95% CI -7 mmHg to -3 mmHg). In ARDS, inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures.

Sawheny et al. hypothesized that nebulized iloprost would improve ventilation-perfusion matching in 20 patients with pulmonary hypertension and ARDS without adversely affecting lung mechanics or systemic hemodynamics (18). With constant ventilator settings, hemodynamics, airway pressures, and gas exchange measured at baseline were compared with values 30 minutes after administration of 10 µg of nebulized iloprost, 30 minutes after a second, larger 20 µg dose of iloprost, and 2 hours after the second dose of iloprost. Baseline PaO_2 improved from 82±13 to 100±25 mmHg after both the first and second doses of iloprost (p<0.01). PaO_2/FiO_2 ratio improved from 177±60 to 213±67 mmHg (p<0.01). $PaCO_2$, peak and plateau airway pressures, systemic blood pressure, and heart rate were not significantly changed after iloprost. The authors concluded that nebulized iloprost may be a useful therapeutic agent to improve oxygenation in patients with ARDS.

Inhaled Nitric Oxide

Inhaled vasodilators, such as inhaled nitric oxide (iNO), cause vasodilation of pulmonary blood vessels in ventilated lung portions resulting in improved ventilation-perfusion mismatch, better oxygenation, and lower pulmonary arterial pressures. They can be useful in patients with hypoxic respiratory failure and pulmonary hypertension who have failed conventional therapies. They are contraindicated in patients with congenital heart disease, methemoglobinemia, or congestive heart failure. The recommended starting dose is 10-20 ppm. An immediate improvement in PaO_2 of ≥ 20 mmHg should be seen to justify continued use given its significant cost. If improvement in pulmonary function is insufficient, consider adding Sildenafil in conjunction with iNO rather than increasing the iNO to higher levels which commonly yield little improvement and increase adverse reactions and cost. If the patient demonstrates no improvement with iNO, it should be discontinued. Rebound pulmonary hypertension can occur upon withdrawal of iNO. Once sustained improvement in PaO_2 is seen (PaO_2 > 120 mmHg for 4 hours), the iNO should be weaned off using the protocol below:

<u>Weaning of iNO therapy</u>

- FiO_2 should be weaned first to ≤ 0.60
- Maintain PaO_2 60-80 mmHg and SpO_2 > 90% during the weaning process
- Incrementally reduce iNO dose by 5 ppm q 4-6 hours until 5 ppm is reached, then 1 ppm q 4-6 hours until off
    - If oxygenation is not maintained, return to previous dose and retry 4-8 hours later
    - At 1 ppm, increase FiO2 10% above current level and discontinue iNO

Adhikari et al. performed a systematic review and meta-analysis of 12 trials randomly assigning 1237 patients to iNO therapy (19). They found iNO to have no significant effect on hospital mortality (RR 1.10, 95% CI 0.94-1.30), duration of ventilation, or ventilator-free days. Patients receiving iNO had an increased risk of renal dysfunction. They concluded that while iNO is associated with limited improvement in oxygenation in patients with ARDS, it confers no mortality benefit.

Bronicki et al. studied 55 children with ARDS enrolled from nine centers (20). Patients were randomized to iNO or placebo and remained on the study drug until death, they were free of ventilator support, or day 28 after the initiation of therapy. There was a trend toward improved oxygenation in the iNO group compared to placebo at 4 hours that became significant at 12 hours. Days alive and ventilator free at 28 days was greater in the iNO group (p=0.05). 92% of the iNO group and 72% of the placebo group (p=0.07) survived. The rate of extracorporeal membrane oxygenation (ECMO)-free survival was significantly greater in those randomized to iNO vs. placebo (92% vs. 52%; p<0.01). The use of iNO was

associated with a significantly reduced duration of mechanical ventilation and significantly greater rate of ECMO-free survival.

Sildenafil

Sildenafil is a newer PDE-5 inhibitor used in the management of erectile dysfunction that acts by increasing the local availability of endogenous NO. Sildenafil has a higher PDE-5 selectivity than dipyridamole and a predictable gastrointestinal absorption making it an attractive complement to iNO for the management of acute pulmonary hypertension in critically ill patients. Rather than simply adding the effect of a second vasodilator, sildenafil may enhance the selective pulmonary vasodilator effect of iNO by making more messenger cGMP available locally (21).

Lee et al. retrospectively evaluated the use of sildenafil to facilitate weaning from iNO after congenital cardiac surgery (22). Oral sildenafil was administered to seven children who had failed attempts at iNO weaning. iNO was weaned from 30±6 ppm prior to sildenafil initiation to 12±3 ppm in the 24 hours after sildenafil (p=0.024). Mean pulmonary artery (29±1 vs. 27±1 mmHg; p=0.07) and systemic arterial pressure (56±1 vs. 54±1 mmHg; p=0.20) were unchanged from baseline when measured one hour after sildenafil dosing. Sildenafil may facilitate withdrawal of iNO and prevent rebound pulmonary hypertension in patients previously failing iNO weaning attempts.

Airway pressure release ventilation (APRV)

APRV is inverse ratio, pressure-controlled, intermittent mandatory ventilation with unrestricted spontaneous breathing. APRV was introduced as an alternative mode of mechanical ventilation (23-25). It has gained popularity as an effective alternative for difficult-to-oxygenate patients with ARDS. Studies evaluating APRV are few, but it can be useful in patients with refractory hypoxemia. The mandatory breaths in APRV are time-triggered, pressure-targeted, time-cycled breaths. Spontaneous breaths can occur both during and between mandatory breaths. The improved oxygenation seen during APRV are attributed to the beneficial effects of spontaneous breathing through better gas distribution and better ventilation/perfusion matching to the poorly aerated dorsal region of the lungs, along with the higher mean airway pressures obtained with pressure-controlled mandatory breaths. APRV has been shown to decrease the need for neuromuscular blockade by 70% and the use of sedation by 40% compared to conventional modes of mechanical ventilation. Because of the benefits of spontaneous breathing, APRV should not be used in patients who require deep sedation or neuromuscular blockade.

There is no consensus in the literature with regard to setting APRV parameters. The necessary ventilatory parameters include the peak inspiratory pressure ("P_{High}"), the lowest expiratory pressure ("P_{Low}"), the time spent at P_{High} ("T_{High}"), and time spent in exhalation ("T_{Low}"). Some recommend constructing a pressure-volume curve and setting the P_{High} below the upper inflection point and the P_{Low} above the lower inflection point of the inspiratory limb of the curve. This method theoretically makes the most physiologic sense and has been studied extensively in conventional mechanical ventilation where optimal PEEP is thought to be best approximated by the lower inflection point. Others recommend setting the P_{High} according to the plateau pressure of the volume-controlled mode or the Paw of the pressure-controlled mode. In general, P_{High} should be limited to 30-35 cmH_2O while setting the P low at zero cmH_2O in conjunction with a very short T_{Low}. The short T_{Low} creates intentional gas trapping (auto-PEEP) to maintain end-expiratory lung volume. This method takes into consideration avoiding excessive inflation pressures, but the resultant tidal volume can be highly variable and may be higher than the accepted standard of care (i.e., 6-8 mL/kg) due to the contribution of the patient's spontaneous inspiratory effort. Initial APRV setting recommendations are below:

Initial APRV settings

- P_{High}: 20-30 cmH_2O
- P_{Low}: 0-5 cmH_2O
- T_{High}: 4-6 seconds
- T_{Low}: 0.2-0.8 seconds

To correct inadequate oxygenation, increase either P_{High}, T_{High}, or both to increase mean airway pressure. To correct inadequate ventilation, increase P_{High} and decrease T_{High} simultaneously to increase tidal volume and minute ventilation while keeping mean airway pressure stable. Alternatively, increase T_{Low} in 0.05-0.1 second increments to increase the amount of time spent in exhalation or decrease sedation to increase the patient's contribution to minute ventilation.

When FiO_2 has been weaned below 0.50, recruitment is maximized, and the patient is breathing spontaneously, weaning from APRV can begin by decreasing the P_{High} by 1-2 cmH_2O and increasing the T_{High} by 0.5 seconds for every 1 cmH_2O drop in P_{High}. This is referred to as the “drop and stretch”. This should be performed every two hours as tolerated. Weaning too quickly can derecruit alveoli and decrease oxygenation. Monitor the patient for increased work of breathing, tachypnea, or decreases in SpO_2. If this occurs, return to the previous settings. When the P_{High} reaches 10 cmH_2O and the T_{High} reaches 12-15 seconds, change the mode to CPAP with PEEP at 10 cmH_2O and Pressure Support at 5-10 cmH_2O and resume conventional ventilator weaning.

Liu et al. retrospectively studied 58 patients with severe ARDS (PaO_2/FiO_2 ratio < 150) who received either SIMV or APRV (26). PaO_2/FiO_2 ratios were statistically higher in the APRV group ($p<0.05$) while vasopressor use was less ($p=0.018$), and mortality tended to be lower compared to the SIMV group (31% vs. 59% ($p=0.05$). Use of APRV in patients with severe ARDS appears to be associated with improvements in oxygenation and a trend toward lower ICU mortality. No significant adverse effects were observed.

Putensen et al. randomized 30 trauma patients to either APRV or pressure-controlled continuous mandatory ventilation (27). They identified that APRV patients had fewer ventilator days (15 vs. 21) and fewer ICU days (23 vs. 30). The authors explained these differences as being due to spontaneous breathing, improved hemodynamics, less sedation, and no paralytic agents used in the APRV group.

Kaplan et al. compared the hemodynamic effects of APRV vs. PC-IRV in patients with ARDS (28). They found significantly higher cardiac index, oxygen delivery, mixed venous oxygen saturation, and urine output, less vasopressor and inotrope usage, and lower lactate concentration and central venous pressure in patients while on APRV.

Bilevel Positive Airway Pressure

Bilevel positive airway pressure (BPAP) is a mode used during noninvasive positive pressure ventilation (NPPV). It delivers a preset inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The tidal volume correlates with the difference between IPAP and EPAP. For example, an IPAP of 15 cm H_2O and EPAP of 5 cm H_2O (difference of 10 cm H_2O) will generate a larger tidal volume than an IPAP of 10 cm H_2O and EPAP of 5 cm H_2O (difference of 5 cm H_2O). Most BPAP devices also permit a backup respiratory rate to be set. Biphasic positive airway pressure (BIPAP) is pressure-controlled ventilation that allows unrestricted spontaneous breathing throughout the respiratory cycle (29). In BiPAP, the circuit switches between a high and low airway pressure in an adjustable time sequence. The I:E ratio and ventilatory frequency can be adjusted to optimize ventilation and oxygenation. If you reverse the I:E ratio then you have APRV. BiLevel is a combination of APRV and BIPAP, mixing spontaneous and mandatory breath types. Inspiratory pressure and time are set by the ventilator while volume and flow are variable according to the patient’s needs. The mandatory breaths are pressure-controlled, and the spontaneous breaths can be pressure supported. In BiLevel, the ventilator cycling between the two pressure levels can be synchronized with the patient’s spontaneous breathing efforts. The advantages of this mode of ventilation are the decreased level of sedation required to facilitate patient acceptance of the ventilator and the concept of a single modality to ventilate the patient. BiLevel may initially be used as pressure-controlled ventilation, weaned to BIPAP and them weaned to CPAP prior to extubation without a mode change on the ventilator. BiLevel can offer full ventilatory support and can then be weaned off as the patient’s ventilatory needs resolve.

Prone Positioning

Placing a patient in the prone position is an adjunctive strategy that has been used to improve oxygenation in patients with severe ARDS, particularly those with refractory hypoxemia. In the prone position, alveolar consolidation redistributes from dorsal (West's Lung Zone I) to ventral (West's Lung Zone III) as the dorsal region tends to reexpand while the ventral zone tends to collapse. Although gravitational influence is similar in both positions, dorsal recruitment usually prevails over ventral derecruitment. The result of prone positioning is that the overall lung inflation is more homogeneous from dorsal to ventral than in the supine position, with more homogeneously distributed stress and strain. As the distribution of perfusion remains nearly constant in both postures, prone positioning usually improves oxygenation. As ventral alveolar collapse will occur over time, the patient must be rotated from supine to prone position and back every few hours to maintain alveolar recruitment. This can be labor-intensive and is best performed by a trained, multidisciplinary team to avoid artificial airway loss and hemodynamic instability.

Five randomized trials investigating the effects of prone positioning on both oxygenation and mortality in adult ARDS have been reported in the peer-reviewed literature. While all trials demonstrated improvements in oxygenation with prone positioning, there was no statistical difference in mortality. The oxygenation benefits of prone ventilation were apparent with the first session in most trials, and the difference in oxygenation between the prone and supine groups tended to increase with the number of sessions. Improvements in oxygenation were often preserved after returning to the supine position (suggesting that once alveoli have reopened, they are more likely to stay open). In addition to its effects on alveolar recruitment and strain, prone positioning may promote pulmonary secretion drainage. There is evidence that specific disease and patient characteristics may predict which patients are most likely to show improved oxygenation with prone ventilation.

> The 2013 Proning Severe ARDS Patients (PROSEVA) trial randomized 466 patients with severe ARDS in European ICUs to early (<36 hours after intubation), lengthy (goal of 16 hours daily), intermittent prone positioning or to a standard supine position (30). Severe ARDS was defined as a PaO_2/FiO_2 ratio of <150 mmHg with FiO_2 > 60% and PEEP ≥ 5 cm H_2O. At 28 days, the prone group had a 51% relative and 17% absolute reduction in all-cause mortality when compared to the supine group (16% vs. 33%). Importantly, PROSEVA incorporated low-tidal ventilation and therapeutic paralysis, suggesting that prone positioning confers a survival benefit beyond that seen with the standard of care. Adverse events more common with prone positioning included unscheduled extubation (13% vs. 11%) and endotracheal tube obstruction (5% vs. 2%).

High-Frequency Ventilation

High-frequency ventilation is any application of mechanical ventilation with a respiratory rate of greater than 100 breaths per minute. This can be achieved with a small tidal volume and rapid respiratory rate with conventional mechanical ventilation, various forms of external chest wall oscillation, high-frequency percussive ventilation, high-frequency jet ventilation, or high-frequency oscillatory ventilation (HFOV), which currently is the form of high-frequency ventilation most widely used in adult critical care. HFOV uses a piston attached to a diaphragm and oscillates it to deliver a fixed small tidal volume (1-2 mL/kg) at 3-10 Hz (or 180-600/min). HFOV oscillates the gas delivered to pressures above and below the Paw. Paw and FiO_2 are the primary determinants of oxygenation, whereas the pressure amplitude of oscillation (DP) and the respiratory frequency are the determinants of CO_2 elimination. The tidal volume varies directly with DP and inversely with frequency. Paw is initially set to a level approximately 5 cmH_2O above that with conventional ventilation, and DP is set to induce "wiggle," which is torso movement visible to the patient's mid-thigh. Much of the pressure applied to the airway is attenuated by proximal airways and does not reach the alveoli, resulting in a small tidal volume that may be less than dead space. The delivery of a small tidal volume and a high Paw may result in improved alveolar recruitment with less risk of over-distension, thus providing improved gas exchange and lung protection. The risks of HFOV include hemodynamic instability especially in hypovolemic patients, barotrauma / volutrauma, and risk of pneumothorax. Multiple prospective randomized clinical trials have failed to demonstrate a survival benefit from HFOV, however, and there is concern that it may increase patient mortality. HFOV currently should not be used in the treatment of refractory hypoxemia due to ARDS.

Derdak et al. designed a multicenter, randomized, controlled trial comparing the safety and effectiveness of HFOV with conventional ventilation in adults with ARDS (31). 148 adults with a PaO_2/FiO_2 ratio ≤ 200 mmHg on ≥ 10 cmH_2O PEEP were randomized to either HFOV (n=75) or conventional ventilation (n=73). Paw was significantly higher in the HFOV group compared with the conventional ventilation group throughout the first 72 hours (p=0.0001). The HFOV group showed early (less than 16 hours) improvement in PaO_2/FiO_2 compared with the conventional ventilation group (p=0.008); however, this difference did not persist beyond 24 hours. Thirty-day mortality was 37% in the HFOV group and was 52% in the conventional ventilation group (p=0.10). The percentage of patients alive without mechanical ventilation at Day 30 was 36% in the HFOV group and 31% in the conventional ventilation group (p=0.69). There were no significant differences in hemodynamic variables, oxygenation failure, ventilation failure, barotrauma, or mucus plugging between treatment groups.

Ferguson et al. completed the 2013 OSCILLATE trial which randomized 548 intubated ICU patients with early moderate to severe ARDS to HFOV or a ventilatory mode similar to that used in ARDSNet with a primary outcome of in-hospital mortality (32). The trial was stopped early because of the interim analysis demonstrating a 12% absolute increase in in-hospital mortality with HFOV (47% vs. 35%). Some criticisms of the study included that the trial was stopped early despite the stopping thresholds not being met and that the high Paw HFOV protocol may have led to worse outcomes than one with lower pressures. The sedation strategy in the HFOV group may have led to higher mortality as patients may have been given higher doses of sedatives and intravenous fluids. Another consideration was the HFOV may have been initiated too late in the patient's clinical course to supply any benefit.

Young et al. performed a multicenter study (OSCAR trial) randomly assigning adults requiring mechanical ventilation for moderate to severe ARDS to undergo either HFOV or usual ventilatory care (33). All patients had a PaO_2/FiO_2 ≤ 200 mmHg and an expected duration of ventilation of at least two days. The primary outcome was all-cause 30-day mortality. There was no significant difference in mortality (41.7% vs. 41.1%; p=0.85). After adjustment for study center, gender, APACHE II score, and initial PaO_2/FiO_2 ratio, the odds ratio for survival in the conventional-ventilation group was 1.03 (95% CI 0.75-1.40; p=0.87).

Independent Lung Ventilation (ILV)

ILV is an advanced ventilatory technique that focuses on oxygenation and ventilation of each individual lung rather than together as a single unit. It can be classified into either anatomical or physiological lung separation. Anatomical lung separation isolates a diseased lung, using an endobronchial blocking balloon placed with a flexible bronchoscope, from contaminating the non-diseased lung. Physiological lung separation ventilates each lung as an independent unit using a double-lumen endotracheal tube. There are clear indications for ILV as a primary intervention and rescue strategy for refractory hypoxemia. Indications for anatomical lung separation include management of massive hemoptysis and interbronchial aspiration of copious secretions as well as whole lung lavage for pulmonary alveolar proteinosis. Anatomical isolation remains a short-term intervention and is not used for prolonged ventilation because infections cannot be reliably localized by blocking balloons and hemoptysis can only be transiently tamponaded. It allows temporary ventilatory support while definitive treatment such as surgery or embolization is instituted.

Physiologic lung separation employs two mechanical ventilators, one dedicated to each lung, and allows differential application of ventilatory support modes and settings based upon each lung's individual requirements (34). Physiologic ILV may be either synchronous, where the two lungs are ventilated at the same rate, or asynchronous where the rates are different. Physiologic ILV is helpful in the presence of bronchopleural fistulas or unilateral pulmonary contusion where the high ventilatory support settings required by a noncompliant lung may result in overdistention and possible ventilator-induced lung injury to the uninjured lung.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is used in specialized centers for neonatal, pediatric, and adult respiratory and cardiac failure. It is a technique that removes blood from the patient and circulates it through an artificial lung with a pump. The

goal of ECMO is to support gas exchange, allowing the intensity of mechanical ventilation to be reduced and thus decreasing the potentially injurious effects of ventilator- induced lung injury until recovery. Veno-arterial access can be used, but veno-venous access is favored for treating acute respiratory failure. Furthermore, ECMO might be considered the definitive rescue therapy for refractory life-threatening hypoxemia since pulmonary gas exchange is not required.

Peek et al. performed a randomized controlled trial of 180 patients comparing ECMO to conventional ventilation (the Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure, or CESAR, trial) (35). Patients randomized to ECMO were transferred to a single center to receive treatment, whereas patients randomized to conventional ventilation remained in regional hospitals. Survival without disability in the group randomized to receive ECMO was 63% at 6 months (regardless of whether they received ECMO) compared with 47% in the control group ($p=0.03$). This was an intention-to-treat analysis, and only 68 of 90 patients who were randomized to receive ECMO received the therapy because of clinical improvement prior to initiating ECMO, death during transfer or within 48 h of transfer, or contraindication to heparin. An important criticism of this study is the lack of standardized management of patients in the control group, whereas many aspects of care, including adherence to low tidal volume ventilation, were protocolized in the ECMO group with significantly higher adherence. Multiple confounding factors in trial design and implementation resulted in an inability for firm conclusions about the value of ECMO to be drawn.

Kolla et al. at the University of Michigan completed a retrospective review of 141 consecutive patients with hypoxic (n=135) or hypercarbic (n=6) respiratory failure referred for ECMO between 1990 and 1996 (36). Overall, the initial PaO_2/FiO_2 ratio was 75 ± 5. Lung recovery occurred in 67% of patients and 62% survived. Forty-one patients improved without ECMO (83% survived) while 100 did not and were supported with ECMO (54% survived). Survival was greater in patients cannulated within 12 hours of arrival (59%) compared with those cannulated after 12 hours (40%, $p<0.05$). Multiple logistic regression identified age, duration of mechanical ventilation before transfer, four or more dysfunctional organs, and the requirement for ECMO as independent predictors of mortality. The authors concluded that early implementation of ECMO is associated with high rates of survival in patients with severe respiratory failure.

Figure 1: Pressure Control Ventilation (PCV) Basics

PCV Basics

- Pressure and inspiratory time are set by the operator.
- Volume and flow are variable according to patient needs.
- Patient can breathe spontaneously during the inspiratory and expiratory phase of the PC mandatory breath cycle.
- An active valve allows free breathing anytime during mandatory breath delivery.
- PCV cannot count or measure spontaneous breaths.
- PCV cannot synchronize transition to PEEP with patient's spontaneous exhalation.

PCV Settings

- Mode = ACV or SIMV
- PI = Inspiratory pressure (above PEEP)
- TI = Inspiratory time [operator can choose to set TE (expiratory time) or I:E ratio instead of TI]
- PEEP
- Respiratory rate (frequency)
- Rise Time %
- Pressure Support (in SIMV) = above PEEP and only during TE

Setting PCV

1. Set desired level of PEEP
2. Set initial rate at 12-14 breaths/minute
3. Adjust inspiratory pressure (IP) to obtain a tidal volume of 6 mL/kg
4. Set initial inspiratory time at 0.5 to 0.8 seconds
5. Set flow triggering
6. Look at pressure waveform, adjust inspiratory flow (slope) to optimal setting
7. Check a blood gas after 30-60 minutes
    a. If $PaCO_2$ is elevated, increase the respiratory rate, but be careful of auto-PEEP
    b. If hypoxemia is improving, reduce the driving (inspiratory) pressure
8. If the patient develops severe hypoxemia
    a. Increase the PEEP as necessary
    b. Increase the inspiratory time to 1.0 to 1.5 seconds to promote alveolar recruitment

REFERENCES

1. Briel M, Meade M, Mercat A, Brower RG, Talmour D, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome. *JAMA* 2010; 303(9):865-873.
2. Halter JM, Steinberg JM, Schiller HJ, dAsILVA m, Gatto LA et al. Positive End-Expiratory Pressure after a Recruitment Maneuver Prevents Both Alveolar Collapse and Recruitment/Derecruitment. *AJRCCM* 2003; 167:
3. Hodgson C, Goligher EC, Young ME, Keating JL, Holland AE, et al. Recruitment manoeuvres for adults with acute respiratory distress syndrome receiving mechanical ventilation. *Cochrane Database Syst Rev* 2016 Nov 17;11.
4. Arnal JM, Paquet J, Wysocki M, Demory D, Donati S, et al. Optimal duration of a sustained inflation recruitment maneuver in ARDS patients. *Intensive Care Med* 2011; 37(10):1588-94.
5. Pelosi P, Cadringher P, Bottino N, Panigada M, Carrieri F, et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; 159:872–880.
6. Lapinsky SE, Mehta S. Bench-to-bedside review: Recruitment and recruiting maneuvers. *Critical Care* 2004 9:60.
7. Lim CM, Jung H, Koh Y, Lee JS, Shim TS, et al. Effect of alveolar recruitment maneuver in early acute respiratory distress syndrome according to antiderecruitment strategy, etiological category of diffuse lung injury, and body position of the patient. *Crit Care Med* 2003, 31:411-418.
8. Constantin JM, Godet T, Jabaudon M, Bazin JE, Futier E. Recruitment maneuvers in acute respiratory distress syndrome. *Ann Transl Med* 2017; 5(14): 290.
9. 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; 342:1301–1308.
10. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; 299(6):637-645.
11. Kallet RH, Campbell AR, Alonso JA, Morabito DJ, Mackersie RC. The effects of pressure control versus volume control assisted ventilation on patient work of breathing in acute lung injury and acute respiratory distress syndrome. *Respir Care* 2000; 45(9):1085-1096.
12. Rappaport SH, Shpiner R, Yoshihara G, Wright J, Chang P, Abraham E. Randomized, prospective trial of pressure-limited versus volume-controlled ventilation in severe respiratory failure. *Crit Care Med* 1994; 22(1):22-32.
13. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107-1116.
14. Alhazzani W, Alshahrani M, Jaeschke R, Forel JM, Papazian L, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2013; 17(2): R43.
15. Zavala E, Ferrer M, Polese G, Masclans JR, Planas M, et al. Effect of inverse I:E ratio ventilation on pulmonary gas exchange in acute respiratory distress syndrome. *Anesthesiology* 1998; 88(1):35-42.
16. Papadakos PJ, Halloran W, Hessney JI, Lund N, Feliciano DV. The use of pressure-controlled inverse ratio ventilation in the surgical intensive care unit. *J Trauma* 1991; 31(9):1211-1214.
17. Fuller BM, Mohr NM, Skrupky L, Fowler S, Kollef MH, et al. The use of inhaled prostaglandins in patients with ARDS: a systematic review and meta-analysis. *Chest* 2015; 147(6):1510-1522.
18. Sawheny E, Ellis AL, Kinasewitz GT. Iloprost improves gas exchange in patients with pulmonary hypertension and ARDS. *Chest* 2013; 144(1):55-62.
19. Adhikari NKJ, Burns KEA, Friedrich JO, Granton JT, Cook DJ, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007; 334(7597): 779.
20. Bronicki RA, Fortenberry J, Schreiber M, Checchia PA, Anas NG. Multicenter randomized controlled trial of inhaled nitric oxide for pediatric acute respiratory distress syndrome. *J Pediatr* 2015; 166(2):365-369.
21. Bigatello LM, Hess D, Dennehy KC. Sildenafil can increase the response to inhaled nitric oxide. *Anesthesiology* 2000; 92:1827-1829.

22. Lee JE, Hillier SC, Knoderer CA. Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. *J Intensive Care Med* 2008; 23(5):329-334.
23. Downs JB, Stock MC. Airway pressure release ventilation: A new concept in ventilatory support. *Crit Care Med* 1987; 15:459–461.
24. Stock MC, Downs JB, Frolicher DA. Airway pressure release ventilation. *Crit Care Med* 1987; 15:462–466.
25. Habashi NM. Other approaches to open-lung ventilation: Airway pressure release ventilation. *Crit Care Med* 2005; 33: S228–240.
26. Liu L, Tanigawa K, Ota K, Tamura T, Yamaga S, et al. Practical use of airway pressure release ventilation for severe ARDS--a preliminary report in comparison with a conventional ventilatory support. *Hiroshima J Med Sci* 2009; 58(4):83-88.
27. Putensen C, Zech S, Wrigge H, Zinserling J, Stüber F, et al. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med* 2001; 164(1):43-49.
28. 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(4):221-226.
29. 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; 14:576–582.
30. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, et al. Prone Positioning in Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2013; 368:2159-2168.
31. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med* 2002; 166(6):801-808.
32. Ferguson ND, Cook DJ, M.D., Guyatt GH, Mehta S, Hand L, et al. High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. *N Engl J Med* 2013; 368:795-805.
33. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, et al. High-Frequency Oscillation for Acute Respiratory Distress Syndrome. *N Engl J Med* 2013; 368:806-813.
34. Cheatham ML, Promes JT. Independent lung ventilation in the management of traumatic bronchopleural fistula. *Am Surg* 2006; 72(6):530-533.
35. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, et al. 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(9698):1351-63.
36. Kolla S, Awad SS, Rich PB, Schreiner RJ, Hirschl RB, et al. Extracorporeal life support for 100 adult patients with severe respiratory failure. *Ann Surg* 1997; 226(4):544-564.

Surgical Critical Care Evidence-Based Medicine Guidelines Committee

Primary Author: Tony Gielow, DO
Co-Authors: None
Editor: Michael L. Cheatham, MD, Chadwick Smith, MD
Last revision date: August 21, 2018

Please direct any questions or concerns to: webmaster@surgicalcriticalcare.net