Mechanical Ventilation in Patients with Acute Respiratory Distress Syndrome

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POSITIVE-PRESSURE mechanical ventilation is essential for keeping alive critically ill patients who have acute respiratory distress syndrome (ARDS), a severe but reversible lung disease characterized by a diffuse injury of the alveolar-capillary barrier. The reported incidence of ARDS ranges between 1.5 and 13.5 per 100,000 population, with a mortality rate of 27–60%. Compelling evidence has progressively emerged suggesting that mechanical ventilation, although indispensable for survival, may be detrimental to the injured lung and may increase mortality rate if inappropriately administered. Ventilatory support, by supplying the deficient lung function until recovery, is aimed at achieving an arterial oxygenation that ensures adequate tissue oxygenation and provides appropriate carbon dioxide elimination. A consensus exists that these clinical objectives should be reached without applying pressures and volumes that are too high to noninjured parts of the lung. The optimum ventilatory strategy in patients with ARDS should represent a compromise between alveolar recruitment and lung overinflation that both result from mechanical ventilation-induced increase in airway pressure. This article provides a critical analysis of recent experimental and clinical studies supporting this concept.

Ventilator-induced Lung Injury

The generic term ventilator-induced lung injury encompasses three different pathologic entities: high-permeability type pulmonary edema; mechanical distortion/overinflation of lung structures; and lung inflammation, the so-called biotrauma. The administration of tidal volumes ranging between 20 and 50 ml/kg to animals with normal or injured lungs produces a protein-rich pulmonary edema that is histologically indistinguishable from other forms of high-permeability-type pulmonary edema. Positive end-expiratory pressure (PEEP) seems partially protective against experimental ventilator-induced pulmonary edema, provided it does not increase inspiratory pressure and contribute to lung overinflation. Experimentally, small animals seem more susceptible than large animals, and end-inspiratory lung volume rather than peak inspiratory pressure seems to be the main causative factor. As a consequence, the term lung volutrauma is more appropriate than lung barotrauma for describing ventilator-induced lung injury. Mechanisms altering the alveolar-capillary barrier permeability during mechanical ventilation are incompletely understood and involve increased transmural vascular pressure, surfactant inactivation, mechanical distortion of endothelial cells, and regional activation of inflammatory cells.

In contrast to mechanical ventilation-induced pulmonary edema that cannot be directly evidenced in humans because it lacks clinical and histologic specificity, overinflation and distortion of lung structures are easy to detect in patients with ARDS. Emphysema-like lesions, lung cysts, and bronchiectasis are frequently found in lung autopsies and can be considered the prominent features of human ventilator-induced lung injury. As demonstrated on thoracic computed tomography imaging performed in late stages of ARDS, these lesions predominate in nondependent and caudal lung regions. They are preceded by lung overinflation that can be evidenced at early stages of the disease in patients with a focal loss of aeration who are receiving high PEEP and tidal volumes. The degree of overinflation is dependent on tidal volume, peak airway pressure, duration of mechanical ventilation, and time exposed to an inspired oxygen fraction (FiO2) greater than 0.6. Recent experimental studies have demonstrated that mechanical ventilation produces air space enlargement. Histologic bronchioloalveolar distension and distortion can be produced by 2 days of mechanical ventilation in piglets with severe focal bron-
Lung Recruitment Aimed at Providing Adequate Arterial Oxygenation

Optimizing lung recruitment in patients with ARDS remains a highly controversial issue. Recruitment of nonaerated lung units, which is basically an inspiratory process resulting from tidal volume administration, can be impaired by reducing tidal volume or amplified by performing a recruitment maneuver. PEEP contributes to lung recruitment by maintaining at end expiration the aeration of lung units that are recruited during the inspiratory phase. More than 10 yr ago, the “open lung concept” was proposed as a strategy aimed at optimizing lung recruitment by reestablishing normal lung aeration: Inspiratory pressures greater than 50 cm H₂O should be first applied during limited periods of time to “open up” nonaerated lung regions (recruitment maneuvers), and subsequently, a PEEP greater than 15 cm H₂O should be maintained to prevent end-expiratory derecruitment. Because of the risk of regional lung overinflation that is inherent in the open-lung concept, a more pragmatic strategy of alveolar recruitment has recently been advocated, taking into consideration lung morphology and the regional distribution of lung aeration for selecting the correct PEEP level. Lung recruitment is no longer aimed at reestablishing normal lung aeration but is performed first and foremost to provide an arterial oxygen saturation of 90% or greater at an FiO₂ of less than 60%, considered protective against oxygen toxicity. In addition, the strategy for recruiting the lung takes into consideration not only the potential for recruitment but also the risk of regional lung overinflation.

The ARDS lung is characterized by an increase in lung density resulting from alveolar edema and inflammation that predominates in cephalic parts of the lungs. At the same time, the resulting loss of aeration surprisingly predominates in caudal and dependent lung regions in patients lying supine. Initially believed to be the consequence of collapse of the lung under its own increased weight, the loss of aeration more likely results from alveolar flooding and external compression of caudal

Fig. 1. Left and right parasagittal anatomical sections showing external forces applied on the lower lobes at end inspiration and end expiration in a patient with acute lung injury in the supine position and mechanically ventilated with positive end-expiratory pressure. On left and right anatomical sections, the liver and spleen are purple; the left and the right ventricles are red; and the upper, middle, and lower lobes are white (aerated lung) or dark gray (consolidated lung). The large blue arrows indicate the direction of the forces resulting from tidal ventilation, whereas the small blue arrows indicate the direction of the forces resulting from positive end-expiratory pressure. The green arrows indicate the direction of the forces exerted by the abdominal content and the heart on the lung. At end expiration, positive end-expiratory pressure is unable to counteract abdominal and cardiac compressions, and the loss of aeration massively involves the right and left lower lobes and dependent segments of the upper lobes. Positive end-expiratory pressure preserves the aeration of the upper and middle lobes and may be associated with local overinflation. At end inspiration, tidal ventilation partially recruits the lower lobes and dependent segments of the upper lobes and may increase lung overinflation in nondependent lung regions. The prone position partially relieves the abdominal compression and entirely relieves the cardiac compression, allowing reaeration of lower lobes.
parts of the lungs (lower lobes) by an enlarged heart and the high pressure exerted by the abdominal content as represented in figure 1. In 75% of patients with ARDS, the upper lobes remain partially or entirely aerated at zero end-expiratory pressure, whereas the lower lobes are essentially nonaerated. In a minority of patients, the loss of aeration is diffuse and homogeneously distributed between cephalic and caudal lung regions, giving the characteristic radiologic pattern of “white lungs.” Differences in lung morphology condition the selection of the optimum PEEP level. When the loss of aeration is diffuse and involves all lung regions, PEEP levels higher than 10 cm H2O can be reasonably applied to optimize lung recruitment because the risk of lung overinflation seems negligible. The lung behaves as a single compartment whose pressure–volume curve is a lung recruitment curve: The slope of the curve is indicative of lung recruitability, whereas the upper inflection pressure indicates the end of recruitment and the beginning of lung overinflation. The open-lung concept may be safely applied to these patients because the risk of regional lung overinflation seems low. In contrast, when the loss of aeration is focally distributed, giving the characteristic radiologic pattern of bilateral basal radiologic infiltrates respecting the upper quadrants, the lung behaves as several compartments that react in the opposite direction to an increase in intrathoracic pressure: The aerated regions tend to be (over)inflated, whereas the nonaerated regions are progressively recruited. Because the aeration loss markedly predominates in caudal and dependent lung regions in most patients with ARDS who are lying in the supine position, recruitment of the lower lobes often results in overinflation of the upper lobes (fig. 1). As a consequence, the high PEEP levels generally required for reaerating the lower lobes may be associated with a significant risk of ventilator-induced lung overinflation. Therefore, PEEP should be deliberately maintained around 10 cm H2O, and in case of persisting hypoxemia, other means improving ventilation/perfusion ratios, such as inhaled nitric oxide, intravenous almitrine, and the prone position, should be preferred for improving arterial oxygenation.

Recruitment maneuvers, all consisting of short-lasting increases in intrathoracic pressures, have been proposed for enhancing alveolar recruitment and improving arterial oxygenation. Sighs can be delivered periodically during tidal ventilation or after an endotracheal suctioning. One or several consecutive sustained inflations consisting of an inspiratory pressure of 40 cm H2O maintained for 40 s can serve as a recruitment maneuver. Stepwise increases and decreases in PEEP to the preset level while maintaining a constant inspiratory pressure of 40 cm H2O is another form of recruitment maneuver. It requires 2 min to perform and provides long-lasting improvement in arterial oxygenation. In fact-depleted collapse-prone lungs, recruitment maneuvers provide a dramatic increase in arterial oxygenation by boosting the ventilatory cycle onto the deflation limb of the pressure–volume curve. However, in different experimental models of lung injury, recruitment maneuvers do not provide similar beneficial effects. In patients with ARDS, recruitment maneuvers are effective in improving arterial oxygenation only at low PEEP and small tidal volumes. When alveolar recruitment is optimized by increasing PEEP, recruitment maneuvers are either poorly effective or deleterious, inducing overinflation of the most compliant lung regions, hemodynamic instability, and an increase in pulmonary shunt resulting from the redistribution of pulmonary blood flow toward nonaerated lung regions. Although recruitment maneuvers are deleterious in patients with head injury, they are efficient for preventing endotracheal suctioning–induced hypoxemia and derecruitment in patients with acute lung injury. Three consecutive sighs per minute allowing peak plateau pressure to reach 45 cm H2O are effective for significantly improving arterial oxygenation in patients with ARDS who are ventilated with a volume-controlled mode with a PEEP of 15 cm H2O and a tidal volume of 7 ml/kg. A single sigh per minute allowing peak plateau pressure to reach 35 cm H2O is also effective for significantly improving arterial oxygenation in patients with ARDS who are ventilated using pressure support ventilation with a PEEP of 10 cm H2O and a tidal volume of 5–6 ml/kg. However, it should be noted that experimental and clinical data on the potential deleterious effects of periodic sighs in terms of lung overinflation are lacking. Systematic administration of recruitment maneuvers cannot be recommended in patients with ARDS and should be restricted to individualized clinical decisions aimed at improving arterial oxygenation in patients who remain severely hypoxemic. For example, recruitment maneuvers are quite efficient for rapidly reversing aeration loss resulting from endotracheal suctioning or accidental disconnection from the ventilator.

In patients at risk of regional overinflation caused by an increase in intrathoracic pressure, prone positioning offers an attractive alternative. Turning the patient in the prone position tends to limit the expansion of cephalic and parasternal lung regions and relieves the cardiac and abdominal compression exerted on the lower lobes. It also makes regional ventilation/perfusion ratios and chest wall elastance more uniform, potentiates PEEP-induced alveolar recruitment, and improves arterial oxygenation. In addition, it facilitates drainage of secretions and potentiates the beneficial effect of recruitment maneuvers, factors that contribute to improve arterial oxygenation in more than 70% of patients with early stage ARDS. After identifying absolute contraindications such as burns and open wounds on the face or ventral body surface, spinal instability, pelvic fractures, life-threatening circulatory shock, and increased intracra-

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nal pressure,\textsuperscript{32} prone positioning can be considered and performed according to a predefined and standardized protocol.\textsuperscript{35} The optimum daily duration of prone positioning is not known. In clinical practice, the duration of prone positioning ranges between 6 and 12 h/day. It is also uncertain whether the abdomen should be suspended during prone positioning. Main complications are facial edema, pressure sores, accidental loss of the endotracheal tube, thoracic and abdominal drains, and central venous catheters. During the period of prone positioning, enteral feeding should be stopped. The total duration and number of pronations depends on the effects on arterial oxygenation of supine repositioning.\textsuperscript{34} Despite its beneficial effects on arterial oxygenation, prone positioning does not increase survival in patients with acute respiratory failure.\textsuperscript{36} However, in the most severely hypoxicemic patients with an arterial oxygen tension (\(P_{aO_2}\))/FiO\(_2\) of less than 100 mmHg, it may reduce mortality and limit ventilator-induced lung injury.\textsuperscript{37} Additional studies are needed to confirm this possibility.

In a limited number of patients, arterial oxygenation remains severely impaired despite PEEP, prone positioning, and recruitment maneuvers. The administration of low doses of inhaled nitric oxide (5 parts per million), intravenous almitrine (2–4 \(\mu g\) · kg\(^{-1}\) · min\(^{-1}\)), or both may markedly increase \(P_{aO_2}\), allowing the use of an FiO\(_2\) lower than 0.6.\textsuperscript{38} By redistributing pulmonary blood flow toward ventilated lung areas through selective vasodilatation or vasoconstriction, both drugs significantly reduce pulmonary shunting, and their effect is additive.\textsuperscript{38,39} In addition, inhaled nitric oxide reduces pulmonary hypertension resulting from permissive hypercapnà\textsuperscript{40} and tends to limit the extension of pulmonary edema.\textsuperscript{31} Prospective randomized multicenter trials have failed to demonstrate an increase in survival rate of patients treated with inhaled nitric oxide in the early phase of acute lung injury.\textsuperscript{42,43} In addition, the beneficial effect on arterial oxygenation is limited to 48 h. As a consequence, inhaled nitric oxide should not be administered systematically but either as a rescue therapy in the most severely hypoxicemic patients or as a complementary therapy in patients with a focal loss of aeration in which a PEEP greater than 10 cm H\(_2\)O cannot be applied without overdistending some parts of the lungs.

**Ventilatory Settings Aimed at Providing Carbon Dioxide Elimination**

Setting the correct tidal volume implies selecting the best compromise between two opposite requirements: Ensure normal carbon dioxide elimination, and avoid ventilator-induced lung injury. Besides tidal volume, respiratory frequency and instrumental dead space volume markedly influence carbon dioxide elimination.\textsuperscript{44} There is compelling experimental and clinical evidence calling for a reduction of tidal volume in patients with ARDS. A single-center study\textsuperscript{45} and a multicenter study\textsuperscript{46} comparing tidal volumes of 12 ml/kg in the control group to tidal volume of 6 ml/kg in the “protected” group demonstrated a significant reduction in the mortality rate of patients treated with low tidal volumes. However, three multicenter randomized studies comparing tidal volumes ranging between 10 and 15 ml/kg in control groups and tidal volumes ranging between 5 and 10 ml/kg in protected groups were negative in terms of mortality.\textsuperscript{37–39} These contradictory results have been the source of an ongoing controversy. As pointed out by some investigators,\textsuperscript{50} plateau airway pressures were different in the control arms of negative and positive trials. In positive trials, tidal volumes were rigidly fixed at 12 ml/kg ideal body weight, resulting in plateau airway pressures that were higher than prerandomization levels (≥ 35 cm H\(_2\)O). In the control groups of the three negative trials, plateau airway pressures were maintained below 35 cm H\(_2\)O by adapting tidal volume between 10 and 15 ml/kg. As a consequence, a possible interpretation of the five randomized trials could be that tidal volumes of 12 ml/kg when associated with inspiratory airway pressures greater than 35 cm H\(_2\)O are harmful. This interpretation challenges the classic view stating that tidal volumes of 6 ml/kg associated with inspiratory airway pressures less than 30 cm H\(_2\)O are beneficial. In addition, a nonsignificant increase in mortality was observed in the low-tidal-volume arm of one of the negative trials,\textsuperscript{48} suggesting that tidal volumes that are too low may be deleterious. Opponents of this interpretation argue that the three negative trials were probably underpowered with an unfavorable signal-to-noise ratio. They also point out that mortality in the control group of the National Institute of Health ARDSnet trial was 40%, a mortality rate similar to that of the control arm in one of the negative trials. Therefore, it seems reasonable to state that 6 ml/kg improves survival, rather than to state that 12 ml/kg increases mortality.\textsuperscript{51–53} It should be noted that the ARDSnet trial provides the strongest evidence that using a tidal volume of 6 ml/kg reduces mortality.

Whatever the quality of exchanged arguments, to date, there is no “magic number,” and the safe level of tidal volume remains to be determined for each patient. According to the existing literature, it seems reasonable to use tidal volumes between 6 and 10 ml/kg if plateau airway pressures are maintained below 30 cm H\(_2\)O. Ideally, the tidal volume should be reduced in each patient according to the proportion of lung accessible to the gas coming from the ventilator. For example, a tidal volume of 8 ml/kg distributed in a lung whose gas volume is reduced by half is equivalent to a tidal volume of 16 ml/kg administered to a normally aerated lung. Unfortunately, apart the quantitative computed tomography approach, which remains time consuming and is
reserved to research protocols and lung ultrasonography, which could be a promising semi-quantitative evaluation tool in a close future.44,55 There is no simple means for determining at the bedside the proportion of aerated lung. Therefore, the determination of the optimal tidal volume for a given patient remains partly empirical, its maximum value being determined by the necessity of limiting plateau airway pressure to 30 cm H2O after the PEEP has been fixed.

Can the pressure–volume curve help in setting tidal volume and PEEP? In a minority of ARDS patients with a diffuse loss of aeration, the pressure–volume curve is a lung recruitment curve whose upper inflection pressure indicates the end of recruitment and the beginning of overinflation.9 As a consequence, the plateau airway pressure resulting from PEEP and tidal volume should remain below the upper inflection pressure. Unfortunately, the majority of patients with ARDS have a focal loss of aeration, and the pressure–volume curve is no longer solely a recruitment curve. Therefore, setting the plateau airway pressure below the upper inflection pressure does not protect against overinflation that may occur in aerated lung regions together with alveolar recruitment of poorly and nonaerated lung regions.

To weaken the deleterious effect of decreasing tidal volume on carbon dioxide elimination, reduction of instrumented dead space and increase in respiratory rate are essential complements. Connecting the Y piece directly to the proximal tip of the endotracheal tube and replacing the heat and moisture exchanger positioned between the endotracheal tube and the Y piece with a conventional humidifier positioned on the initial part of the inspiratory limb contribute to improving carbon dioxide elimination by reducing instrumental dead space and carbon dioxide rebreathing. In many patients with ARDS, the respiratory system is abnormally stiff, and the time required for a given tidal volume to be expired is shortened. As a consequence, the respiratory frequency of the ventilator can be increased to 20–30 breaths/min without generating intrinsic PEEP. As far as respiratory frequency is concerned, there is no “magic number.” The physician should progressively increase respiratory rate while looking at the screen of the ventilator displaying inspiratory and expiratory flows: As long as expiratory flow remains nil at end expiration, respiratory rate can be increased without generating intrinsic PEEP. Because increasing respiratory rate must be performed at constant inspiratory/expiratory ratio and tidal volume to avoid intrinsic PEEP, peak airway pressure tends to increase, whereas plateau airway pressure remains unchanged. Combining the reduction of instrumental dead space with the maximum increase in respiratory frequency that does not generate intrinsic PEEP may result in an arterial carbon dioxide tension reduction as large as 40%.44

Maintenance of a Spontaneous Breathing Activity

There is increasing experimental and clinical evidence suggesting that spontaneous breathing should not be totally suppressed in patients with ARDS receiving mechanical ventilation.56 Administering partial ventilatory support to patients with severe acute pulmonary dysfunction challenges the classic view considering full ventilatory support and deep sedation as accepted standards for the early phase of ARDS. During biphasic positive airway pressure, beneficial increases in ventilation/perfusion ratios, arterial oxygenation, and cardiac output have been evidenced in patients with ARDS who are spontaneously breathing as compared with deeply anesthetized patients.57,58 Pressure support ventilation, another form of partial ventilatory support, seems less efficient than biphasic positive airway pressure58,59 in terms of arterial oxygenation but may provide a substantial improvement in carbon dioxide elimination. Although the mechanisms of these improvements are not fully elucidated, a likely hypothesis is that the active diaphragmatic contraction contributes to the reaeration of the lower lobes, which remain nonaerated in many patients with ARDS who are lying in the supine position.8,18,23 It is well known that the diaphragmatic displacement resulting from an active muscular contraction predominates in dependent lung regions, whereas mechanical ventilation–induced passive diaphragmatic displacement predominates in nondependent lung regions.60 In fact, not only cardiac and abdominal compressions but also deep sedation and full ventilatory support contribute to the dramatic loss of aeration characterizing the lower lobes of patients with ARDS. Maintaining some degree of spontaneous breathing likely allows partial reaeration of lower lobes. To ensure some degree of spontaneous breathing, sedation should be titrated to a Ramsay score of 2 or 3 corresponding to a partial awake state. Further randomized multicenter studies are needed to demonstrate that the maintenance of a spontaneous breathing activity is associated with a decrease in mortality, a shorter duration of mechanical ventilation, and a reduced duration of stay in the intensive care unit.

In conclusion, mechanical ventilation of patients with ARDS requires a specific adjustment of ventilatory settings. Increases in intrathoracic pressures aimed at optimizing lung recruitment should take into consideration not only the potential for recruitment of the nonaerated lung but also the risk of overinflation of lung regions remaining fully aerated at zero end-expiratory pressure. Based on the assessment of the individual lung morphology, selecting the correct PEEP level should result from a compromise between recruitment of dependent and caudal lung regions (lower lobes) and overinflation of nondependent and cephalic lung regions (upper and middle lobes). Prone positioning, by changing the pattern of stress applied to the lung, may facilitate PEEP-
induced lung recruitment of the lower lobes. Recruitment maneuvers are efficient for reestablishing lung aeration after acute episodes of derecruitment. Of particular importance is the recommendation of using tidal volumes of less than 10 ml/kg to maintain plateau airway pressure below 30 cm H₂O. Reduction of instrumental dead space, increases in respiratory frequencies without producing intrinsic PEEP, and maintenance of a spontaneous breathing pattern seem to be useful complements to ensure adequate carbon dioxide elimination, enhance lung recruitment of the lower lobes, and limit the cardiovascular effects of positive-pressure ventilation. A logical sequence of steps for selecting the correct ventilatory settings in patients with ARDS is proposed in figure 2.

Fig. 2. Algorithm for selecting appropriate ventilatory settings in patients receiving mechanical ventilation for acute respiratory distress syndrome (diagnostic steps in yellow, ventilatory settings in red, and therapeutic targets in green). BIPAP = biphase positive airway pressure; CT = computed tomography; \( P_{100} \) = inspired positive airway pressure; \( P_{FIO2} \) = arterial carbon dioxide tension; \( P_{SV} \) = pressure-volume support ventilation; \( P_{PV} \) = pressure–volume; \( SaO2 \) = oxygen saturation measured by pulse oximetry; \( VCV \) = volume control ventilation; ZEEP = zero end-expiratory pressure.

References

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54. Hubmayr RD: The times are a-changin’. Should we hang up the stethoscope? Anesthesiology 2004; 100:1–2.


