An approach to ventilation in acute respiratory distress syndrome

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Appropriate management of patients with acute respiratory distress syndrome (ARDS) represents a challenge for physicians working in the critical care environment. Significant advances have been made in understanding the pathophysiology of ARDS. There is also an increasing appreciation of the role of ventilator-induced lung injury (VILI). VILI is most likely related to several different aspects of ventilator management: barotrauma due to high peak airway pressures, lung overdistension or volutrauma due to high transpulmonary pressures, alveolar membrane damage due to insufficient positive end-expiratory pressure levels and oxygen-related cell toxicity. Various lung protective strategies have been suggested to minimize the damage caused by conventional modes of ventilation. These include the use of pressure- and volume-limited ventilation, the use of the prone position in the management of ARDS, and extracorporeal methods of oxygen delivery and carbon dioxide removal. Although the death rate resulting from ARDS has been declining over the past 10 years, there is no evidence that any specific treatment or change in approach to ventilation is the cause of this improved survival.

La prise en charge appropriée des patients souffrant d'insuffisance respiratoire aiguë pose un défi aux médecins qui travaillent aux soins intensifs. On a fait des progrès importants pour mieux comprendre la pathophysiologie de cette affection respiratoire. On comprend également mieux le rôle des atteintes pulmonaires attribuables à un respirateur (APAR). Une APAR est fort probablement liée à plusieurs aspects différents de la gestion de la ventilation : barotraumatisme attribuable à une pression maximale élevée dans les voies aériennes, surdistension pulmonaire ou volutraumatisme découlant d'une pression transpulmonaire élevée, lésions de la membrane alvéolaire provenant d'une pression positive insuffisante en fin d'expiration et toxicité cellulaire liée à l'oxygène. On a proposé diverses stratégies de protection pulmonaire pour réduire les dégâts causés par les pratiques classiques de ventilation, notamment : ventilation à pression ou volume limité, position couchée pour la prise en charge de l'insuffisance respiratoire aiguë et méthodes extracorporelles d'apport d'oxygène et d'élimination du dioxyde de carbone. Même si le taux de décès attribuable à l'insuffisance respiratoire aiguë diminue depuis 10 ans, rien ne prouve que cette amélioration résulte d'un traitement spécifique ou d'une nouvelle approche de la ventilation.

Over the past 10 years there have been significant changes in the approach to ventilating patients with acute respiratory distress syndrome (ARDS), driven by an evolving body of knowledge of the respiratory mechanics of ARDS and recognition of the potential for ventilator-induced lung injury (VILI).

In 1994 a consensus conference of American and European investigators agreed that ARDS should be regarded as the most severe acute lung injury.[1] These investigators also agreed that the diagnostic criteria for ARDS should include the following: acute onset; bilateral chest infiltrates; pulmonary artery occlusion pressure (PAOP) of 18 mm Hg or less or no evidence of left atrial hypertension; impaired oxygenation regardless of the level of positive end-expiratory pressure (PEEP) with a ratio of partial pressure of oxygen in arterial blood (Pa_{O_2}) to fractional intake of oxygen (F_{IO_2}) of less than 200. Using these criteria, Luce[2] found that the incidence of ARDS was between 5 and

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8 per 100 000 population annually.The consensus conference divided the risk factors associated with the development of ARDS into direct and indirect mechanisms of lung injury. The direct mechanisms include gastric aspiration, diffuse pulmonary infection and near drowning. The indirect mechanisms are those due to sepsis, thoracic trauma, multisystem trauma and the effects of multiple transfusions. Of these risk factors, sepsis is most commonly identified in association with ARDS.

The hallmark pathological finding in ARDS is diffuse alveolar damage with an increase in pulmonary membrane permeability. This results in bilateral interstitial and intra-alveolar edema.[3] Alveoli are compressed or flooded, and the surface available for gas exchange is considerably reduced by atelectasis. Vascular congestion and hemorrhage are present. As the disease progresses there is evidence of hyaline membrane formation, and eventually pulmonary fibrosis and capillary obliteration occur.[2]

During the acute stage, diffuse atelectasis, alveolar wall damage, hyaline membrane formation, congestion and increased cellularity of the alveolar walls are evident. The open alveoli allow gas exchange and the fluid-filled alveoli are potentially recruitable with PEEP.[4] In the later proliferative, reparative stage, patchy areas of fibrosis are interspersed with open residual and regenerative air spaces. In this phase the patient is less likely to be responsive to PEEP.[5] Also during this phase, neutrophils and macrophages become sequestered in the pulmonary capillaries. As these cells occlude the pulmonary vasculature, capillary resistance increases and leads to further aggregation of platelets and inflammatory cells, which ultimately increases pulmonary vascular resistance.[5]

Inflammatory cytokines play a significant part in ARDS, but their exact role has not been completely identified.[5] Thrombin, fibrin degradation products and other components of the coagulation cascade interact with neutrophils to mediate endothelial damage. Altered surfactant composition, metabolism and inactivation by serum proteins are some of the recognized mechanisms of surfactant dysfunction in ARDS. Additionally the alveolar epithelium, which normally plays a role in the immune function of the lung and in optimizing ventilation–perfusion matching, is severely damaged in the course of ARDS.[6]

Severe hypoxemia is both a hallmark and a criterion for ARDS. It is caused by intrapulmonary shunting and $\dot{V}/\dot{Q}$ mismatch due to alveolar edema and atelectasis. Even though all lung regions tend to sustain injury more or less uniformly at first, regional micromechanics vary even in the earliest phase of the process. Gravitationally dependent regions are extensively consolidated and atelectatic whereas nondependent regions tend to aerate better. In severe cases, no more than one-third of the alveoli may remain patent. Thus, at least in the early nonfibrotic stage, lungs in ARDS are small rather than stiff. For this condition, Gattinoni and associates[7] coined the term "baby lung." Pulmonary gas exchange is more or less normal in the remaining lung if overdistension and alveolar hyperventilation are avoided. As long as fibrosis has not occurred, the fluid-filled or compressed alveoli are potentially recruitable with the use of PEEP.

VENTILATOR-INDUCED LUNG INJURY

VILI is best understood as a spectrum of lung injuries caused by mechanical ventilation. Classically, VILI was most often recognized clinically as injury from barotrauma. This may present as pneumomediastinum, pneumothorax, pneumoperitoneum, subcutaneous emphysema, pulmonary interstitial emphysema, systemic gas embolism or tension cyst and bullae. These forms of VILI are generally not thought to occur until airway pressures exceed 50 cm H_2O.[8] It has now been recognized that VILI can manifest itself as high permeability pulmonary edema, hyaline membrane formation, decreased lung compliance, atelectasis, alveolar hemorrhage and basement membrane injury. These are the same pathologic changes seen in ARDS.

One of the earliest studies to address the role of pressure in VILI was done by Webb and Tierney in 1974.[9] They demonstrated that when normal rats were ventilated with airway pressures exceeding 30 cm H_2O, pulmonary edema developed. These animals were also exposed to large tidal-volume ventilation, with the tidal volumes used ranging from 29 to 45 mL/kg. Other animal studies have shown that high-pressure ventilation results in endothelial disruption, an increase in microvascular permeability, high permeability alveolar edema, epithelial disruption and hyaline membrane formation.[10,11] Since this form of VILI was associated with high inflation pressures it was thought to be a form of barotrauma. Similar types of airway damage have been found to occur when high tidal volumes without excessive inflation pressures are used — the damage due to overdistension has been termed volutrauma.[8]

The key factor leading to VILI is most likely the transpulmonary pressure to which the alveoli are exposed. Lung overdistension is thought to occur whenever the transpulmonary pressure is greater than 30 to 35 cm H_2O.[4] The point of overdistension can be measured with the aid of a static pressure-volume curve (Fig. 1). On the inspiratory limb there is a point at which compliance suddenly worsens — the upper inflection point. For most patients ventilated with conventional tidal volumes, the upper inflexion point is not exceeded and the lung is not overdistended. How-

ever, in the acute stage of ARDS overdistension can occur at much lower tidal volumes since only a small portion of the lung participates in gas exchange — the baby-lung concept. If a small amount of the healthy lung in the nondependent region is exposed to the tidal volume usually reserved for the entire lung, overdistension and VILI can occur.

Animal experiments have shown that the addition of PEEP significantly reduces alveolar hemorrhage and other histologic changes that are caused by high tidal volumes and transpulmonary pressures.[12] PEEP can prevent or reverse alveolar collapse, increase functional residual capacity and decrease lung water. A lower inflection point in the static pressure–volume curve can be identified in some patients early in the course of ARDS. If PEEP is not maintained above this level, collapsible alveoli will wink open and close during each tidal cycle, generating shear stresses and causing lung injury.[4]

Because of the inhomogeneous nature of the lung involvement in ARDS, the same PEEP that is needed to open and recruit some alveoli will at the same time overdistend others. Whether PEEP adds to the end-expiratory volume of units that are already open or maintains patency of unstable alveoli depends on the patient, the stage of the disease and the vertical position of the alveolus in the injured lung. In a severely injured lung with a vascular bed that is significantly reduced in capacity, PEEP may increase pulmonary vascular resistance and increase edema formation. PEEP's effectiveness in improving oxygen exchange tends to decline as ARDS progresses to the proliferative reparative stage, and in late-stage ARDS high levels of PEEP increase the risk of barotrauma.

High oxygen concentrations have long been known to be toxic to cells and tissues. Oxygen toxicity is believed to be in part related to the production of oxygen free radicals, which are extremely reactive and may cause cellular injury. Bronchoalveolar lavage data have suggested that exposure to oxygen concentrations of 50% for only 44 hours can induce lipid peroxidation, stimulate macrophage release of leukotrienes and increase neutrophil aggregation.[5] Levels of oxygen that have been considered "safe" may therefore have to be reconsidered in the management of ventilated patients.

LUNG-PROTECTIVE VENTILATION STRATEGIES

Better understanding of the pathophysiology of ARDS and of VILI led to the suggestion that airway pressure and tidal volume should be limited in managing the ventilation of patients with ARDS.[13] This type of approach has been termed a lung-protective ventilation strategy (LPVS) (Table I).

Pressure-controlled ventilation, pressure-regulated volume-controlled ventilation, and airway-pressure-release ventilation are all pressure-targeted strategies. Pressure-targeted ventilatory modes emphasize the maintenance of alveolar pressure below the pre-selected airway pressure. In that sense they may be safer than more traditional volume-targeted modes. Because inspiratory pressure remains constant in these modes of ventilation, some lung units that require high and sustained pressures to open may eventually be recruited.

Several well-conducted prospective randomized controlled studies of patients at risk for ARDS have failed to

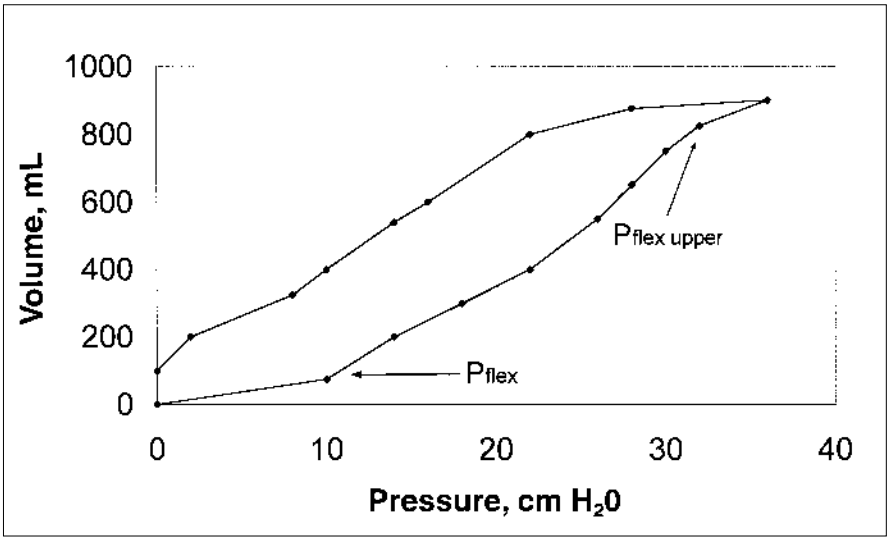

FIG. 1. Lung compliance curve. P_{flex} = lower inflection point, $P_{flex\ upper}$ = upper inflection point.

Table I

Lung Protective Ventilation Strategies

Strategy	Ventilatory management
Avoid regional overdistension Avoid barotrauma	Transpulmonary pressure < 35 cm H_2O to avoid upper inflection point
Avoid repeated opening/closing of airway	PEEP above lower inflection point
Avoid oxygen toxicity	FIO_2 as low as possible

PEEP = positive end-expiratory pressure, FIO_2 = fractional intake of oxygen.

show a difference between pressure- and volume-limited ventilation groups and control groups in which patients were ventilated with tidal volumes of 10 to 15 mL/kg and had peak airway pressures up to 60 cm H_2O.[14–16] No improvement in outcome with respect to barotrauma, days of ventilation and death rate in the patients who were treated with an LPVS was found. Plateau pressures in the control groups were below 35 cm H_2O and as such may have been low enough to prevent progressive lung injury. An LPVS may be beneficial in patients with severe lung disease as indicated by particularly low total lung compliance and chest-wall compliance. A large scale study that may answer this question is presently under way.

Amato and associates have done several studies[17,18] to test the hypothesis that the lung can be protected from injury by limiting distending volume and pressure and by maintaining a level of PEEP that prevents the majority of alveolar units from collapsing at end-exhalation. This strategy was associated with an improvement in survival to 28 days but not with improved survival to hospital discharge. Most of the survival benefit was noted in the first 3 days of mechanical ventilation. If such a strategy prevents lung injury one would expect improvement in survival to be seen later in the course of the disease.

Inverse-ratio ventilation has been proposed as a mechanism for improving gas exchange in patients with ARDS. Prolonging inspiration may ensure more homogeneous ventilation and recruit alveoli with long time constants. Shortened expiratory times will create intrinsic or auto-PEEP, which may improve functional residual capacity and ventilation–perfusion matching. Several studies have failed to show any short- or long-term benefit to inverse-ratio ventilation.[19,20]

The problem of overdistension has led clinicians to speculate that the cost of maintaining a normal partial pressure of carbon dioxide ($PaCO_2$) in the range of 35 to 45 mm Hg is too great and that minute ventilation should be reduced to avoid lung injury. Permissive hypercapnia is not a ventilation strategy in itself but rather a potential component of an LPVS. Permissive hypercapnia has long been accepted as the standard of practice in ventilated patients with airflow obstruction, but it has only recently been recommended in the treatment of patients with ARDS. Lower tidal volumes, airway pressures and respiratory rates may be used if it is accepted that $PaCO_2$ can intentionally rise to non-physiologic levels. Hickling and associates[21,22] reported on a ventilation strategy for ARDS that incorporated permissive hypercapnia with $PaCO_2$ levels being allowed to rise as high as 150 mm Hg. A marked reduction in the death rate to 16% was achieved compared with an expected death rate of 39.6%. This trial has been criticized because it was neither randomized nor controlled. More recent randomized controlled trials in patients having ARDS have shown better evolution of lung function in those treated with an LPVS but no significant improvement in outcome.[23]

A growing interest in therapeutic positioning of patients has been stimulated by the observation that prone positioning of patients with early ARDS can improve PaO_2:FIO_2 ratio by up to 70%.[24] The effects of "proning" may last after the patient has been returned to the supine position. The prone position is considered beneficial because it generates a transpulmonary pressure sufficient to exceed airway opening pressure in dorsal lung regions where atelectasis, shunt and $\dot{V}/\dot{Q}$ mismatch occur. Proning may also protect against the dependent damage induced by the same ventilation pattern in supine patients although to date evidence for this has only been demonstated in dog models.[25] Hypotension, desaturation and arrhythmias may occur during the transition from supine to prone and back, and attention must be given to preserving the position and patency of intravascular lines and the endotracheal tube during the turning process.

Partial substitution for the lung's gas exchange function can reduce the requirement for ventilation. Methods that have been used include extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal. ECMO was tested in a large trial in the 1970s, and no significant improvement in the death rate was found.[26] Interest in this technique continues as a means of supporting patients with intractable hypoxemia, although the benefit has never been clearly shown. In 1986, Gattinoni and colleagues[27] reported a decreased death rate in patients with ARDS who received low-frequency positive-pressure ventilation with extracorporeal carbon dioxide removal by a simple venovenous technique. Extracorporeal carbon dioxide removal is now used in several European centres to treat ARDS just as ECMO is still used in North America largely in treating neonatal respiratory distress syndrome. A randomized trial of extracorporeal carbon dioxide removal compared with pressure-control inverse-ratio ventilation showed no difference in outcome between the 2.[28]

An alternative to allowing permissive hypercapnia or using extrapulmonary techniques for gas exchange in ARDS is to enhance the efficiency of carbon dioxide elimination by tracheal insufflation of fresh gas.[29] This minimally invasive approach reduces the concentration of carbon dioxide in the anatomic dead space. Tracheal insufflation of fresh gas has the potential to cause mucosal damage, retention of secretions and barotrauma. This modality may prove beneficial as an adjunct to an LPVS although its benefit is unproven.

CONCLUSIONS

Studies have shown that over the last 10 years death rates in ARDS have declined by approximately 20%.[30] However, it has never been shown that a specific treatment or change in therapy is the cause of this improved survival. Because of better understanding of the pathophysiology of ARDS and the consequences of VILI, practice patterns with respect to pressure and volume during mechanical ventilation have changed. However, there is little evidence that these new approaches benefit patients. Stewart and colleagues[15] concluded his study on a pressure-limited ventilation strategy by suggesting that "clinicians should proceed with caution when using pressure- and volume-limited ventilation as a routine measure in ventilated patients." Whether such strategies benefit patients with the most severe forms of ARDS is yet to be proven. It must be remembered that patients are individuals and do not behave in any predictable fashion. Proper mechanical ventilation requires repeated bedside reassessment by the critical care team in order to optimize care for the individual patient.

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