Ventilator-Associated Lung Injury during Assisted Mechanical Ventilation

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Mechanical ventilation (MV) is the main form of advanced life support in the intensive care unit. However, even though MV improves gas exchange, keeps the lungs open, and reduces the work of breathing, it may also cause ventilator-associated lung injury (VALI). In the present review, we discuss VALI in relation to assisted MV strategies, such as volume assist–control ventilation, pressure assist–control ventilation, pressure support ventilation (PSV), airway pressure release ventilation (APRV), APRV with PSV, proportional assist ventilation (PAV), noisy ventilation, and neurally adjusted ventilatory assistance (NAVA). In summary, we suggest that assisted MV can be used in ARDS patients in the following situations: (1) PaO2/FIO2 >150 mm Hg and positive end-expiratory pressure ≥ 5 cm H2O and (2) with modalities of pressure-targeted and time-cycled breaths including more or less spontaneous or supported breaths (A-PCV [assisted pressure-controlled ventilation] or APRV). Furthermore, during assisted MV, the following parameters should be monitored: inspiratory drive, transpulmonary pressure, and tidal volume (6 mL/kg). Further studies are required to determine the impact of novel modalities of assisted ventilation such as PAV, noisy pressure support, and NAVA on VALI.
During recent years, there have been many experimental and clinical studies regarding the use of different modes of assisted ventilation in ARDS, such as volume assist–control ventilation, pressure assist–control ventilation, pressure support ventilation (PSV), airway pressure release ventilation (APRV), biphase positive airway pressure and its variants (BIPAP [Dräger, Medical AG, Lübeck, Germany], Bivent [MAQUET, Rastatt, Germany], and Bilevel [Covidien, Mansfield, MA]) with or without PSV, proportional assist ventilation/proportional pressure support (PAV/PPS), noisy ventilation, and neurally adjusted ventilatory assistance (NAVA). In the present review, we provide an update on the recent literature focusing on assisted MV and VALI.

Ventilator-Associated Lung Injury

The histological changes observed in VALI are nonspecific but similar to those of ARDS. There is a direct relationship between histological findings, duration of MV, and the intensity of the injury-producing process. MV with high P<sub>i</sub> can lead to alveolar injury characterized by the presence of hyaline membrane, alveolar hemorrhage, and neutrophilic infiltration. A few minutes after the beginning of MV with high airway pressures, endothelial and epithelial lesions can be visualized by electron microscopy, including disruption of type II pneumocytes, detachment of basement membrane, endothelial disruption, and alveolar edema (Fig. 1). With the progression of lung injury, proliferation of fibroblasts and type II pneumocytes is also observed, as seen in late-stage ARDS.

The lungs are protected against edema formation by three components: capillary filtration pressure, ability of the interstitial space to absorb and buffer extravascular fluids, and ability of the pulmonary lymphatic system to transport fluid out of the lung. MV with high peak inspiratory pressure may induce pulmonary edema even in intact animals or exacerbate edema in the presence of preexisting lung damage. MV-induced pulmonary edema results from changes in the permeability of the alveolar–capillary barrier and extracellular matrix and from lung epithelial and endothelial cell damage. Moreover, regional differences in pulmonary perfusion and atelectasis may lead to increased filtration forces in specific alveolar–capillary units, yielding edema formation. VALI also compromises the ability of the lung to reabsorb fluid through the inhibition of active transport of Na<sup>+</sup> and reduced Na<sub>1</sub>K-ATPase activity in type II pneumocytes.

MV may produce changes in surface area and increased protease activity, leading to conversion of surfactant from large (functionally superior) to small (functionally inferior) aggregates and causing: (1) higher alveolar surface...

Fig. 1  Electron microscopy of lung parenchyma from lung sections of five animals per group. White arrows: alveolar capillary basement (ACB) membrane. Endothelial cells, alveolar types I and II epithelial cells were damaged. ALIexp: extrapulmonary acute lung injury; ALIp: pulmonary acute lung injury; BIVENT: biphase positive airway pressure; Cap: capillary; NV: nonventilated; P2: type II epithelial cell; PCV: pressure-controlled ventilation. (Image courtesy: Prof. Vera Capelozzi.)
tension and epithelial permeability.\textsuperscript{20} (2) collapse of alveoli and peripheral airways with unequal expansion of lung units, thus increasing regional stress,\textsuperscript{21} and (3) increased vascular filtration promoting edema formation.\textsuperscript{31}

**Determinants of Ventilator-Associated Lung Injury**

**Barotrauma and Volutrauma**

High-pressure MV induces rupture of air spaces and hence barotrauma.\textsuperscript{22} Even though the absolute pressure in the airways is not harmful in itself,\textsuperscript{23} the term volutrauma was adopted because P\textsubscript{a} determines VALI.\textsuperscript{24,25} Patients with ARDS are more susceptible to alveolar overdistension, especially when submitted to high tidal volume (V\textsubscript{T}) with conventional MV (10–15 mL/kg) because the number of alveolar units available to be ventilated is reduced due to fluid accumulation, consolidation, and atelectasis.\textsuperscript{26} Low V\textsubscript{T} ventilation reduces the mortality rate in patients with ARDS\textsuperscript{27,28}, even though a V\textsubscript{T} of 6 mL/kg is not necessarily safe, it provides a better prognosis than a V\textsubscript{T} of 12 mL/kg.

**Atelectrauma and Biotrauma**

MV with low volumes at end expiration can also induce lung damage due to the opening and closing of distal airways, ducts, and/or alveolar units. Atelectrauma injury resulting from the repetitive collapse and reopening of alveoli (recruitment and derecruitment) during MV triggers shear stress in the extracellular matrix and in epithelial and endothelial cells, leading to VALI.\textsuperscript{21}

The classic concept of barotrauma implies that injury occurs only when stress/strain is high enough to rupture the lung; however, since the early 1990s, several studies have suggested that nonphysiological stress/strain can promote the release of proinflammatory cytokines and neutrophilic recruitment, leading to lung inflammation even in the absence of structural damage.\textsuperscript{29} The term biotrauma describes a process of injury in which biophysical forces can alter the normal physiology of lung cells, increasing the levels of inflammatory mediators and promoting changes in the process of repair/remodeling of lung tissue. Clinical and experimental studies have shown that injurious ventilation strategies can initiate or perpetuate a local and systemic inflammatory response, which, in turn, can contribute significantly to multiple organ dysfunction syndrome.\textsuperscript{30} Accordingly, several studies have shown that protective ventilation reduces the levels of proinflammatory mediators.\textsuperscript{31–33} In this context, the mechanisms involved in the peripheral organ dysfunction observed in VALI have been associated with inflammatory cascades in lung tissue, including translocation of mediators, endotoxins, and bacteria from the lung to the systemic circulation.\textsuperscript{34}

**The Role of Assisted Mechanical Ventilation in Ventilator-Associated Lung Injury**

Assisted MV is a mode of respiratory support that allows different degrees of inspiratory and/or expiratory effort in each breath. An assisted MV breath is composed of inspiratory trigger, pressure or flow rate, level of inspiratory support, expiratory trigger, and positive end-expiratory pressure (PEEP). The pressure or flow rate, the level of inspiratory support, and the expiratory trigger determine inspiratory time, V\textsubscript{T}, and inspiratory effort. All these parameters must be coordinated with the patient’s inspiratory neuromuscular drive and respiratory mechanics to guarantee patient–ventilator synchronization. Different modalities of assisted MV might reduce stress and/or strain\textsuperscript{35,36} as well as the opening and closing of collapsed peripheral airways and/or atelectatic lung regions, and improve the redistribution of pulmonary perfusion,\textsuperscript{37,38} thus decreasing the damage of alveolar epithelial and endothelial cells as well as extracellular matrix (\textemdash Fig. 2).

Assisted MV has been suggested to minimize the development of VALI by: (1) recruitment-dependent atelectatic lung regions, reducing opening and closing during tidal breath, thus limiting stress and/or strain; (2) distributing regional P\textsubscript{a} and pleural pressures (P\textsubscript{pl}) in a more homogeneous manner; (3) increasing the variability of breathing pattern; (4) redistributing perfusion toward nonatelectatic injured areas; and (5) improving lymphatic drainage.

Transpulmonary pressure is the difference between the pressure inside the alveoli (P\textsubscript{aw}) and P\textsubscript{pl}. There are important differences between the effects of P\textsubscript{aw} and P\textsubscript{pl} in CMV and assisted MV (\textemdash Fig. 3). During CMV, P\textsubscript{pl} depends on V\textsubscript{T}, lung impedance; perfusion increases in dependent lung regions, with collapse of the lymphatic system. Assisted ventilation may or may not be associated with homogeneous lung recruitment (\textemdash Fig. 3). In the presence of lung recruitment, end-expiratory lung volume increases, thus reducing strain, while lung elastance decreases, resulting in lower inspiratory transpulmonary pressure and stress. In the absence of lung recruitment, transpulmonary pressure might be higher than during CMV. However, the redistribution of regional blood flow toward nondependent areas may minimize lung damage, since regional P\textsubscript{pl} is more negative in nondependent areas.

Conversely, spontaneous breathing during assisted MV may exacerbate lung injury by increasing patient–ventilator asynchrony and rapid shallow breathing.\textsuperscript{39} In addition, negative P\textsubscript{pl} may increase intrathoracic blood volume, worsening pulmonary edema, and lung damage.\textsuperscript{40}

**Fig. 2** Assisted mechanical ventilation attenuates VALI decreasing the damage to alveolar epithelial and endothelial cells and extracellular matrix.
In ARDS patients, the combination of neuromuscular blocking agents with volume assist–control ventilation has reduced lung inflammation. In severe ARDS, the use of neuromuscular blocking agents in the first 48 hours of volume assist–control ventilation has decreased mortality. Volume assist–control ventilation may also cause stacked breaths or patient/ventilator asynchrony, suggesting that this ventilation mode should be avoided in the first 48 hours of severe ARDS.

**Pressure Assist–Control Ventilation**

In pressure assist–control ventilation, inspiratory flow is delivered at a variable rate and with a decelerating pattern. Inspiration can be triggered by the patient’s inspiratory effort and time cycling. VT depends on the patient’s impedance and inspiratory effort. Therefore, there is no guarantee that VT is in a protective range. Also, patient/ventilator synchrony cannot be controlled, which may increase the risk of VALI.

The presence of spontaneous breathing during pressure assist–controlled ventilation depends on the severity of lung damage. Spontaneous breathing seems beneficial to recruitment in surfactant depletion–induced mild ARDS. Conversely, in severe experimental ARDS, spontaneous breathing could worsen lung damage, suggesting the use of muscle paralysis to prevent the increase in transpulmonary pressure. Interestingly, spontaneous breathing has been reported to cause a Pendelluft phenomenon in a patient with lung injury receiving assisted pressure controlled ventilation (PCV). The Pendelluft phenomenon consisted of shifts of alveolar air from nondependent to dependent lung regions without a change in VT.

During protective MV in ARDS patients, the comparison between PCV and volume-controlled ventilation (VCV) yields controversial results that depend on flow rate. PCV offers no advantage in reducing work of breathing compared with VCV with a high flow rate, whereas PCV reduces work of breathing when inspiratory flow during VCV does not match the patient’s demand.

**Pressure Support Ventilation**

PSV, the most common mode of assisted MV, is characterized by: (1) same level of Paw supporting each breath, (2) pressure support triggered by either Paw or flow during inspiration, and (3) cycling-off typically occurring at a fixed percentage of peak flow. PSV may result in reduced VALI, since it improves patient–ventilator synchrony, reduces work of breathing, and prevents fatigue of respiratory muscles. However, typical cyclic-off settings of PSV are associated with shorter inspiratory times, resulting in decreased mean Paw and thus potentially leading to lung derecruitment (Fig. 4).

**Airway Pressure Release Ventilation**

APRV is described as continuous positive airway pressure (CPAP) with an intermittent pressure release phase. The presence of an activated expiratory demand valve allows APRV to apply a continuous airway pressure (P_{high}) identical to CPAP to maintain adequate lung volume and promote ventilation/perfusion match.
APRV parameters controlled by clinicians are $P_{\text{high}}$, $T_{\text{high}}$, $P_{\text{low}}$, and $T_{\text{low}}$. Time parameters ($T_{\text{high}}$ and $T_{\text{low}}$) in APRV are very well controlled, allowing a precise adjustment. The $P_{\text{high}}$ and $T_{\text{high}}$ regulate end-inspiratory lung volume and provide a significant contribution to mean airway pressure. Mean airway pressure is critical for maintaining an increased area of open air spaces for gas exchange. As a result, these parameters control oxygenation and alveolar ventilation. APRV adds a time-cycled release phase to a lower set pressure ($P_{\text{low}}$). In addition, spontaneous breathing can be integrated and is independent of ventilator cycle. CPAP breathing mimics the gas distribution of spontaneous breaths as opposed to mechanically controlled, assisted, or supported breaths, which produce less physiological distribution. Mechanical (or controlled) breaths shift ventilation to nondependent lung regions, whereas spontaneous breathing during APRV results in a more dependent gas distribution and less shear stress.

The clinical trials conducted using APRV compared with other modes of ventilation showed the following results favoring APRV: (1) lower airway pressures to sustain similar or better oxygenation; (2) better V/Q, less dead space, and better compliance; (3) less hemodynamic impairment with higher cardiac output and oxygen delivery, less need of vasopressors; (4) shorter duration of intubation and need less of sedation; and (5) fewer intensive care unit and ventilation days.

However, to date, no clinical trial has evaluated the relationship between APRV and VALI. In this scenario, our group investigated the effects of APRV associated with a protective strategy (limited $P_{\text{paw}}$, low $V_T$, and $P_{\text{low}}$ to keep lungs open) in experimental ARDS. We observed that, in experimental models of mild pulmonary and extrapulmonary ARDS, APRV led to less biological impact on lung tissue compared with PCV, regardless of the etiology of lung damage.

**Airway Pressure Release Ventilation with Pressure Support Ventilation**

Currently, some ventilator manufacturers incorporate the possibility of activating PSV above $P_{\text{low}}$ (BIPAP, Dräger) or $P_{\text{low}}$ and $P_{\text{high}}$ (Bivent, Maquet and Bilevel, Covidien). The addition of PSV above $P_{\text{high}}$ may increase transpulmonary pressure, thus improving lung recruitment (~Fig. 4). On the contrary, the addition of PSV may contradict the purposes of APRV, which are the reduction of airway pressure and the limitation of lung distension. Moreover, the major advantage of APRV is the preservation and promotion of spontaneous breathing, and the addition of PSV to APRV may eliminate these benefits by altering the shape of inspiratory flow curve (from sinusoidal to decelerating pattern). In addition, PSV associated with APRV may lead to air trapping and asynchrony, with negative effects on lung mechanics, work of breathing, and hemodynamic parameters. Finally, the improvement in V/Q by APRV may be reduced when PSV is added.

A recent study from our group evaluated the effects of APRV associated with PSV in experimental ARDS. APRV + PSV showed better functional results with less lung damage and expression of inflammatory mediators compared with PCV. Although the addition of PSV to APRV seems to be safe, the optimal level of PSV to optimize lung function minimizing the risk of VALI requires further investigation.

**Proportional Assist Ventilation/Proportional Pressure Support**

PAV/PPS generates positive pressure throughout inspiration in proportion to patient-generated flow and volume. Therefore, the ventilator is able to deliver flow and volume according to the patient's ventilatory demand and respiratory mechanics (respiratory system elastance and resistance). In contrast to PAV, in PAV +, the mechanical properties of the respiratory system are continuously assessed, improving patient/ventilator synchrony; nevertheless, $V_T$ may be outside the protective range, causing VALI. A recent experimental study has reported no significant difference between conventional pressure support and PAV concerning lung mechanics, histology, and inflammation in experimental ARDS induced by saline lung lavage.

**Noisy Ventilation**

During PSV, spontaneous breaths are supported by a fixed pressure support, which may yield a respiratory pattern with relatively low $V_T$ variability. However, decreased variability

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**Fig. 4** Tracing of tracheal pressure during pressure support ventilation (PSV) and airway pressure release ventilation (APRV) + PSV. Note the reduced inspiratory time and mean airway pressure during PSV.
of V̇T has been shown to be associated with impaired lung function and increased lung damage. Experimental studies have shown that the combination of assisted MV and variable V̇T by means of variable pressure support levels (variable PSV, noisy PSV) may improve lung function and reduce lung inflammation. Noisy PSV can increase the variability of the respiratory pattern even when it is intrinsically reduced, as often seen in critically ill patients. A recent clinical study tested the safety and feasibility of noisy PSV in patients with acute hypoxemic respiratory failure. Noisy PSV was not associated with any adverse event and was well tolerated by all patients. Noisy PSV increased the variability of V̇T and was associated with reduced asynchrony compared with conventional PSV.

An ongoing randomized controlled trial focusing on patients during weaning from MV is comparing the effects of conventional versus variable pressure support on the time to successful weaning, defined as the time from randomization to successful extubation.

### Neurally Adjusted Ventilatory Assistance

NAVA delivers pressure to the airways proportional to inspiratory diaphragmatic electrical activity (EAdi). The proportionality factor is set on the ventilator by the clinician (NAVA gain). EAdi is influenced by facilitatory and inhibitory, vagally mediated feedback loops that integrate information from mechano- and chemoreceptors that “sense” the degree of lung stretch, as well as chemical stimuli. EAdi is upregulated if the delivered V̇T is below the subject’s respiratory demand and downregulated if the assist is greater than the subject’s demand. When the assist level with NAVA satisfies the subject’s respiratory demand, V̇T remains virtually unchanged despite increases in the proportionality factor.

NAVA provides assist on a breath-by-breath basis in synchrony with and in proportion to the patient’s respiratory demand. Experimental and clinical studies demonstrate that NAVA may be effective in patients with increased work of breathing and/or respiratory muscle weakness. Moreover,

### Table 1 The experimental studies demonstrate the effect of assisted ventilation to lung injury

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Abbreviations: A-PCV, assisted pressure controlled ventilation; APRV, airway pressure release ventilation; ARDS, acute respiratory distress syndrome; NAVA, neurally adjusted ventilatory assistance; PCV, pressure controlled ventilation; PSV, pressure support ventilation; VALI, ventilator-associated lung injury; V̇T, tidal volume.
NAVA prevents excessive lung distension, efficiently unloads respiratory muscles, and improves patient–ventilator synchrony.85,86

To evaluate whether NAVA reduces VALI, an experimental study was conducted comparing NAVA with CMV with low \( V_T \) (6 mL/kg) and high \( V_T \) (15 mL/kg) in hydrochloric acid–induced ARDS in rabbits.87 It was observed that in rabbits, NAVA is as effective to prevent VALI as ventilation with low \( V_T \). Certainly, further studies should be conducted in larger animals as well as in the clinical setting (Table 1).

**Conclusion**

Assisted MV has been used for mild and moderate ARDS, because it may minimize the development of VALI by increasing lung volume and reducing the amount of opening and closing of peripheral airways and atelectasis, thus decreasing strain and stress, respectively. Conversely, assisted MV may increase patient–ventilator asynchrony, which may result in higher transpulmonary pressure and rapid shallow breathing with further atelectasis and tidal recruitment–derecruitment, thus leading to VALI.

In ARDS patients, we suggest that assisted MV: (1) be applied in patients with \( P_{\text{aO}_2} \) higher than 150 mm Hg with PEEP higher or equal to 5 cm H\(_2\)O; (2) should be used in modalities of pressure-targeted and time-cycled breaths, including more or less spontaneous or supported breaths (pressure assist–control ventilation or APRV). Furthermore, during assisted MV, the following parameters should be monitored: inspiratory drive, transpulmonary pressure, and \( V_T \) (6 mL/kg predicted body weight). Further evidence is required to determine the impact of novel modalities of assisted ventilation, such as PAV, NAVA, and noisy pressure support on VALI. Randomized controlled trials are warranted to clearly define the role of assisted MV in different degrees of ARDS.

**References**

20. Albert RK. The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. Am J Respir Crit Care Med 2012;185(7):702–708


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


Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? Respir Care 2012;57(2):282–292


Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe acute respiratory failure. Chest 1991;100(2):460–463


Chanques G, Kress JP, Pohlman A, et al. Impact of ventilator adjustment and sedation-analgesia practices on severe...
74 Spieth PM, Carvalho AR, Güldner A, et al. Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. Crit Care Med 2011;39(4):746–755
78 Kiss T, Güldner A, Bluth T, et al. Rationale and study design of ViPS - variable pressure support for weaning from mechanical ventilation: study protocol for an international multicenter randomized controlled open trial. Trials 2013;14:363