Ventilator-Associated Lung Injury during Assisted Mechanical Ventilation

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Abstract

Assisted mechanical ventilation (MV) may be a favorable alternative to controlled MV at the early phase of acute respiratory distress syndrome (ARDS), since it requires less sedation, no paralysis and is associated with less hemodynamic deterioration, better distal organ perfusion, and lung protection, thus reducing the risk of 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) $Pa_{O_2}/F_{I_{O_2}}$ >150 mm Hg and positive end-expiratory pressure $\geq$ 5 cm H_2O 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.

Keywords
- acute respiratory distress syndrome
- assisted mechanical ventilation
- ventilator-associated lung injury
- transpulmonary pressure

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).[1–4]

In critically ill patients with acute respiratory distress syndrome (ARDS), full control of stress and strain may be achieved with controlled MV (CMV) under deep sedation with and without paralysis.[5] However, patients on CMV are not capable of reversing alveolar collapse in lower posterior lung areas and are at increased risk of ventilator-induced diaphragmatic dysfunction.[6] Furthermore, CMV may deteriorate cardiocirculatory performance and impose long-term ventilator dependence, causing complications such as ventilator-associated pneumonia.

In the early phase of ARDS, or in hemodynamically stable patients with mild to moderate ARDS, assisted ventilation may be an option instead of CMV. Some of the benefits described for this mode of ventilatory support are related to reduced sedation requirements, no need for paralysis, less hemodynamic deterioration, better distal organ perfusion, and lung protection. However, during respiratory muscle contraction, assisted ventilation may induce an unpredictable increase in transpulmonary pressure (P_L), possibly associated with increased lung injury.[5,7]

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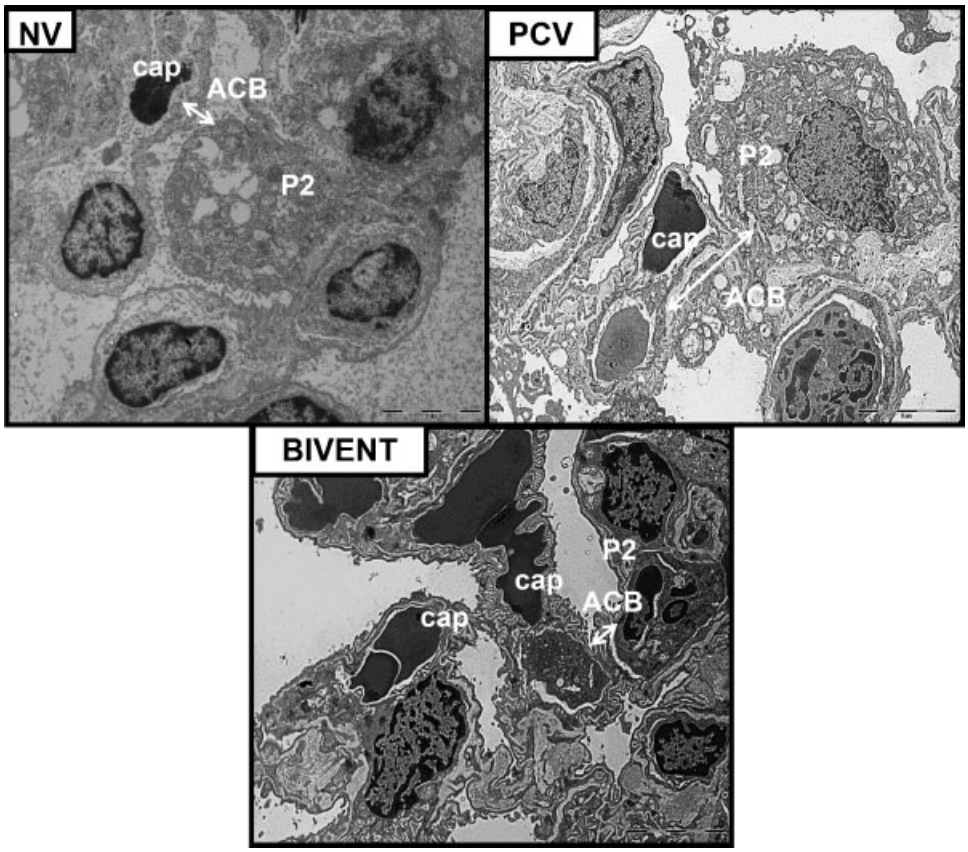

Fig. 1 Electron microscopy of lung parenchyma from lung sections of five animals per group. White arrows: alveolar capillary basement (ACB) membrane. Endothelial cells, alveolar types I and II epithelial cells were damage. ALIexp: extrapulmonary acute lung injury; ALIp: pulmonary acute lung injury; BIVENT: biphasic positive airway pressure; Cap: capillary; NV: nonventilated; P2: type II epithelial cell; PCV: pressure-controlled ventilation. (Image courtesy: Prof. Vera Capelozzi.)

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), biphasic 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.[3,8] There is a direct relationship between histological findings, duration of MV, and the intensity of the injury-producing process. MV with high P_L can lead to alveolar injury characterized by the presence of hyaline membrane, alveolar hemorrhage, and neutrophilic infiltration.[9] A few minutes after the beginning of MV with high airway pressures, endothelial and epithelial lesions can be visualized by electron microscopy,[8,10] including disruption of type II pneumocytes,[11] detachment of basement membrane, endothelial disruption, and alveolar edema[12] (►**Fig. 1**). With the progression of lung injury, proliferation of fibroblasts and type II pneumocytes is also observed, as seen in late-stage ARDS.[11,13]

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[9] or exacerbate edema in the presence of preexisting lung damage.[1] 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.[14,15] 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^+ and reduced Na, K-ATPase activity in type II pneumocytes.[16,17]

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[18,19] and causing: (1) higher alveolar surface

tension and epithelial permeability,[20] (2) collapse of alveoli and peripheral airways with unequal expansion of lung units, thus increasing regional stress,[21] and (3) increased vascular filtration promoting edema formation.[11]

Determinants of Ventilator-Associated Lung Injury

Barotrauma and Volutrauma

High-pressure MV induces rupture of air spaces and hence barotrauma.[22] Even though the absolute pressure in the airways is not harmful in itself,[23] the term volutrauma was adopted because P_L determines VALI.[24,25] Patients with ARDS are more susceptible to alveolar overdistension, especially when submitted to high tidal volume (V_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.[26] Low V_T ventilation reduces the mortality rate in patients with ARDS[27,28]; even though a V_T of 6 mL/kg is not necessarily safe, it provides a better prognosis than a V_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 cycles 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.[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.[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.[30] Accordingly, several studies have shown that protective ventilation reduces the levels of proinflammatory mediators.[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.[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_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[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,[37,38] thus decreasing the damage of alveolar epithelial and endothelial cells as well as extracellular matrix (►**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_L and pleural pressures (P_{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_{aw}) and P_{pl}. There are important differences between the effects of P_{aw} and P_{pl} in CMV and assisted MV (►**Fig. 3**). During CMV, P_{pl} depends on V_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 (►**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_{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.[39] In addition, negative P_{pl} may increase intrathoracic blood volume, worsening pulmonary edema, and lung damage.[40]

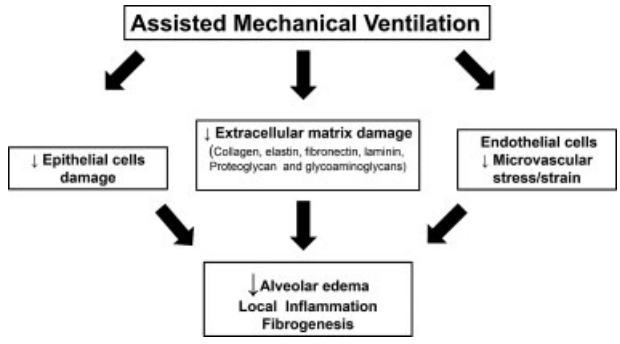

Fig. 2 Assisted mechanical ventilation attenuates VALI decreasing the damage to alveolar epithelial and endothelial cells and extracellular matrix.

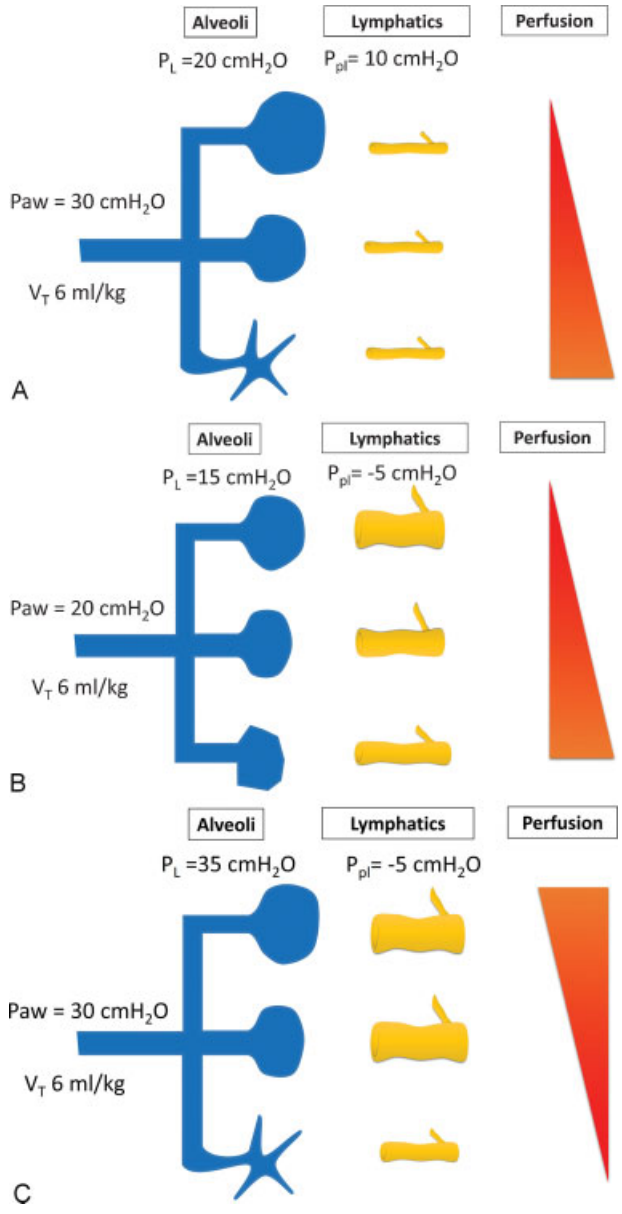

Fig. 3 Schematic representation of alveoli under different mechanical ventilation strategies: pressure controlled ventilation, and pressure assist ventilation (recruited and nonrecruited) under the same tidal volume (V_T). Transpulmonary pressure (P_L) is the difference between the pressure inside the alveoli (P_{aw}) and P_{pl}. (Panel A) During controlled mechanical ventilation, P_{pl} was positive, perfusion increased toward the dependent lung regions, and lymphatic vessels were collapsed. (Panel B) During assisted ventilation, when homogeneous alveoli were recruited, both lung strain and stress were reduced due to the increase in end-expiratory lung volume and to the reduction in inspiratory P_L, respectively. (Panel C) In the absence of lung recruitment, P_L was higher than during controlled mechanical ventilation, regional blood flow was redistributed toward nondependent areas, and lymphatic vessels remained open.

Volume Assist–Control Ventilation

In volume assist–control ventilation, a fixed V_T is delivered in time-cycled manner in response to inspiratory activity. In a retrospective study, low V_T during volume assist–control ventilation was not associated with increased need for sedation[41] or neuromuscular blocking agents.[42]

In ARDS patients, the combination of neuromuscular blocking agents with volume assist–control ventilation has reduced lung inflammation.[7] In severe ARDS, the use of neuromuscular blocking agents in the first 48 hours of volume assist–control ventilation has decreased mortality.[5] Volume assist–control ventilation may also cause stacked breaths[43] 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. Ventilation can be triggered by the patient's inspiratory effort and time cycling.[44] V_T depends on the patient's impedance and inspiratory effort. Therefore, there is no guarantee that V_T 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.[45] 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 V_T.[46]

During protective MV in ARDS patients, the comparison between PCV and volume-controlled ventilation (VCV) yields controversial results that depend on flow rate.[47,48] PCV offers no advantage in reducing work of breathing compared with VCV with a high flow rate,[48] whereas PCV reduces work of breathing when inspiratory flow during VCV does not match the patient's demand.[47]

Pressure Support Ventilation

PSV, the most common mode of assisted MV,[49] is characterized by: (1) same level of P_{aw} supporting each breath, (2) pressure support triggered by either P_{aw} 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 P_{aw} 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.[50] 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.

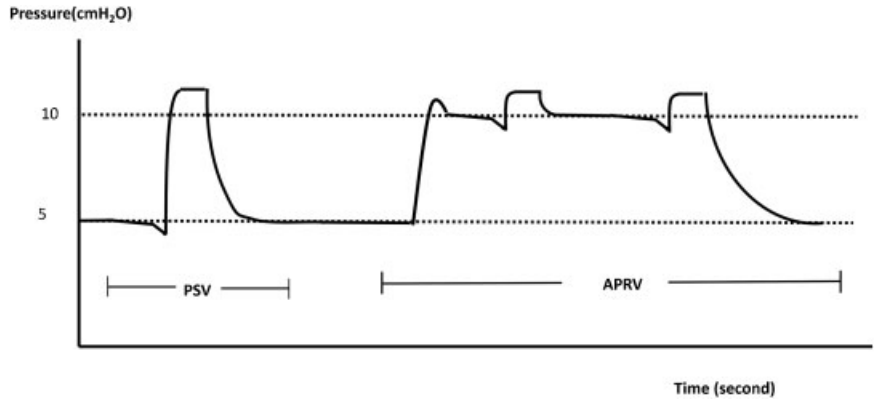

Fig. 4 Tracing of tracheal pressure during pressure support ventilation (PSV) and airway pressure release ventilation (APRV) + PSV. Note the reduced inspiratory time and mean airway pressure during PSV.

APRV parameters controlled by clinicians are P_{high}, T_{high}, P_{low}, and T_{low}. Time parameters (T_{high} and T_{low}) in APRV are very well controlled, allowing a precise adjustment. The P_{high} and T_{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_{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.[51–53] 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.[36]

The clinical trials conducted using APRV compared with other modes of ventilation showed the following results favoring APRV[51,54–59]: (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 less need 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_L, low V_T, and P_{low} to keep lungs opened) in experimental ARDS.[60] 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_{low} (BIPAP, Dräger) or P_{low} and P_{high} (Bivent, Maquet and Bilevel, Covidien).[61] The addition of PSV above P_{high} may increase transpulmonary pressure, thus improving lung recruitment (►**Fig. 4**).[62] 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.[63,64] 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.[62] 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,[65,66] improving patient/ventilator synchrony[67]; nevertheless, V_T may be outside the protective range, causing VALI.[68] 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.[69]

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.[70] However, decreased variability

of V_T has been shown to be associated with impaired lung function and increased lung damage.[71–73] Experimental studies have shown that the combination of assisted MV and variable V_T by means of variable pressure support levels (variable PSV, noisy PSV) may improve lung function and reduce lung inflammation.[37,74,75] Noisy PSV can increase the variability of the respiratory pattern even when it is intrinsically reduced, as often seen in critically ill patients.[76] A recent clinical study tested the safety and feasibility of noisy PSV in patients with acute hypoxemic respiratory failure.[77] Noisy PSV was not associated with any adverse event and was well tolerated by all patients. Noisy PSV increased the variability of V_T 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.[78]

Neurally Adjusted Ventilatory Assistance

NAVA delivers pressure to the airways proportional to inspiratory diaphragmatic electrical activity (EAdi).[79] 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.[80–82] EAdi is upregulated if the delivered V_T is below the subject's respiratory demand and downregulated if the assist is greater than the subject's demand.[80–84] When the assist level with NAVA satisfies the subject's respiratory demand, V_T remains virtually unchanged despite increases in the proportionality factor.[80–84]

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

References	Mode of MV	VALI impact	Major remarks
Saddy et al[60]	APRV	Less biological impact on lung tissue	In mild pulmonary and extrapulmonary endotoxin–induced ARDS, APRV improved lung function and reduced VALI compared with PCV ($V_T \leq 6$ mL/kg)
Saddy et al[62]	APRV + PSV	Less biological impact on lung tissue	In mild paraquat-induced ARDS, APRV + PSV led to more beneficial effects than PCV and A-PCV ($V_T \leq 6$ mL/kg)
Xia et al[53]	APRV	Attenuated biological impact on normal lung	In healthy lungs, APRV resulted in less biological impact compared with controlled mechanical ventilation. Preserving spontaneous breathing attenuate selected markers of VALI
Spieth et al[74]	PSV and noisy PSV	Attenuation of lung inflammation better in noisy PSV compared with PSV	In surfactant depletion–induced ARDS, PSV and noisy PSV attenuated pulmonary inflammatory response and improved gas exchange as compared with PCV
Brander et al[87]	NAVA	Prevented VALI and attenuated excessive systemic and remote organ inflammation	In experimental hydrochloric acid–induced ARDS, NAVA was as protective as controlled mechanical ventilation ($V_T \leq 6$ mL/kg)
Yoshida et al[86]	A-PCV	Low V_T associated with spontaneous breathing resulted in the best compliance and lung aeration but worsen lung damage	In surfactant depletion–induced mild ARDS, even when plateau pressure is limited to < 30 cm H_2O, strong spontaneous breathing effort increases transpulmonary pressure and worsens lung injury
Yoshida et al[45]	A-PCV	The benefits of spontaneous breathing depend on the severity of lung injury	In surfactant depletion–induced mild ARDS, spontaneous breathing was beneficial to recruitment. Conversely, in severe ARDS spontaneous breathing could worsen lung damage

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; V_T, tidal volume.

NAVA prevents excessive lung distension, efficiently unloads respiratory muscles, and improves patient–ventilator synchrony.[45,80,81,83–86]

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) can be applied in patients with Pa_{O_2} F_{IO_2} higher than 150 mm Hg with PEEP higher or equal to 5 cm H_2O; (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

1 de Prost N, Ricard JD, Saumon G, Dreyfuss D. Ventilator-induced lung injury: historical perspectives and clinical implications. Ann Intensive Care 2011;1(1):28
2 Gattinoni L, Protti A, Caironi P, Carlesso E. Ventilator-induced lung injury: the anatomical and physiological framework. Crit Care Med 2010;38(10, Suppl):S539–S548
3 Rocco PR, Dos Santos C, Pelosi P. Pathophysiology of ventilator-associated lung injury. Curr Opin Anaesthesiol 2012;25(2): 123–130
4 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369(22):2126–2136
5 Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107–1116
6 Jaber S, Petrof BJ, Jung B, et al. Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 2011;183(3):364–371
7 Forel JM, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34(11): 2749–2757
8 Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988;137(5):1159–1164
9 Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 1974;110(5):556–565
10 Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985; 132(4):880–884
11 Maron-Gutierrez T, Pelosi P, Rocco PRM. Ventilator-induced lung injury. In: Ferrer M, Pelosi P eds. New Developments in Mechanical Ventilation. European Respiratory Society monographs. Plymouth, UK: European Respiratory Society; 2012:1–18
12 dos Santos CC, Slutsky AS. The contribution of biophysical lung injury to the development of biotrauma. Annu Rev Physiol 2006; 68:585–618
13 Curley GF, Contreras M, Higgins B, et al. Evolution of the inflammatory and fibroproliferative responses during resolution and repair after ventilator-induced lung injury in the rat. Anesthesiology 2011;115(5):1022–1032
14 Pelosi P, Rocco PR. Effects of mechanical ventilation on the extracellular matrix. Intensive Care Med 2008;34(4):631–639
15 Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. Am J Respir Crit Care Med 1998; 157(1):294–323
16 Sartori C, Matthay MA. Alveolar epithelial fluid transport in acute lung injury: new insights. Eur Respir J 2002;20(5):1299–1313
17 Lecuona E, Saldías F, Comellas A, Ridge K, Guerrero C, Sznajder JI. Ventilator-associated lung injury decreases lung ability to clear edema in rats. Am J Respir Crit Care Med 1999;159(2): 603–609
18 Dreyfuss D, Soler P, Saumon G. Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. J Appl Physiol (1985) 1992;72(6):2081–2089
19 Malloy JL, Veldhuizen RA, Lewis JF. Effects of ventilation on the surfactant system in sepsis-induced lung injury. J Appl Physiol (1985) 2000;88(2):401–408
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
21 Pelosi P, Rocco PR. Airway closure: the silent killer of peripheral airways. Crit Care 2007;11(1):114
22 Slutsky AS. Ventilator-induced lung injury: from barotrauma to biotrauma. Respir Care 2005;50(5):646–659
23 Bouhuys A. Physiology and musical instruments. Nature 1969; 221(5187):1199–1204
24 Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008; 359(20):2095–2104
25 Sarge T, Talmor D. Transpulmonary pressure: its role in preventing ventilator-induced lung injury. Minerva Anestesiol 2008;74(6): 335–339
26 Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 2001;164(9):1701–1711
27 [Anonymous]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(18):1301–1308
28 Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338(6):347–354
29 Tremblay LN, Slutsky AS. Ventilator-induced injury: from barotrauma to biotrauma. Proc Assoc Am Physicians 1998;110(6): 482–488

30 Brégeon F, Delpierre S, Chetaille B, et al. Mechanical ventilation affects lung function and cytokine production in an experimental model of endotoxemia. Anesthesiology 2005;102(2):331–339
31 Wolthuis EK, Choi G, Dessing MC, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. Anesthesiology 2008;108(1):46–54
32 Michelet P, D'Journo XB, Roch A, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology 2006;105(5):911–919
33 Parsons PE, Eisner MD, Thompson BT, et al; NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005;33(1):1–6, discussion 230–232
34 Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med 2006;32(1):24–33
35 Gama de Abreu M, Pelosi P, Rocco PRM. Pros and Cons of Assisted Mechanical Ventilation in Acute Lung Injury. In: Vincent JL ed. Annual Update in Intensive Care and Emergency Medicine. Mörlenbach, Germany: Strauss GmbH. 2011:159–173
36 Gama de Abreu M, Cuevas M, Spieth PM, et al. Regional lung aeration and ventilation during pressure support and biphasic positive airway pressure ventilation in experimental lung injury. Crit Care 2010;14(2):R34
37 Carvalho AR, Spieth PM, Güldner A, et al. Distribution of regional lung aeration and perfusion during conventional and noisy pressure support ventilation in experimental lung injury. J Appl Physiol (1985) 2011;110(4):1083–1092
38 Carvalho AR, Spieth PM, Pelosi P, et al. Pressure support ventilation and biphasic positive airway pressure improve oxygenation by redistribution of pulmonary blood flow. Anesth Analg 2009; 109(3):856–865
39 Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 2006;32(10):1515–1522
40 Kallet RH, Alonso JA, Luce JM, Matthay MA. Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a low-tidal volume, lung-protective ventilator strategy. Chest 1999; 116(6):1826–1832
41 Kahn JM, Andersson L, Karir V, Polissar NL, Neff MJ, Rubenfeld GD. Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. Crit Care Med 2005;33(4): 766–771
42 Cheng IW, Eisner MD, Thompson BT, Ware LB, Matthay MA; Acute Respiratory Distress Syndrome Network. Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. Crit Care Med 2005;33(1):63–70, discussion 239–240
43 Pohlman MC, McCallister KE, Schweickert WD, et al. Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. Crit Care Med 2008;36(11):3019–3023
44 Nichols D, Haranath S. Pressure control ventilation. Crit Care Clin 2007;23(2):183–199, viii–ix
45 Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. Crit Care Med 2013;41(2):536–545
46 Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. Am J Respir Crit Care Med 2013;188(12):1420–1427
47 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
48 Kallet RH, Campbell AR, Dicker RA, Katz JA, Mackersie RC. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. Respir Care 2005;50(12):1623–1631
49 Esteban A, Anzueto A, Frutos F, et al; Mechanical Ventilation International Study Group. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002;287(3):345–355
50 Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? Respir Care 2012;57(2):282–292
51 Putensen C, Zech S, Wrigge H, 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
52 Wrigge H, Zinserling J, Neumann P, et al. Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. Anesthesiology 2003;99(2):376–384
53 Xia J, Sun B, He H, Zhang H, Wang C, Zhan Q. Effect of spontaneous breathing on ventilator-induced lung injury in mechanically ventilated healthy rabbits: a randomized, controlled, experimental study. Crit Care 2011;15(5):R244
54 Varpula T, Jousela I, Niemi R, Takkunen O, Pettilä V. Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury. Acta Anaesthesiol Scand 2003;47(5):516–524
55 Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettilä VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesthesiol Scand 2004;48(6):722–731
56 Räsänen J, Cane RD, Downs JB, et al. Airway pressure release ventilation during acute lung injury: a prospective multicenter trial. Crit Care Med 1991;19(10):1234–1241
57 Cane RD, Peruzzi WT, Shapiro BA. Airway pressure release ventilation in severe acute respiratory failure. Chest 1991;100(2): 460–463
58 Fan E, Khatri P, Mendez-Tellez PA, Shanholtz C, Needham DM. Review of a large clinical series: sedation and analgesia usage with airway pressure release and assist-control ventilation for acute lung injury. J Intensive Care Med 2008;23(6):376–383
59 Dart BW IV, Maxwell RA, Richart CM, et al. Preliminary experience with airway pressure release ventilation in a trauma/surgical intensive care unit. J Trauma 2005;59(1):71–76
60 Saddy F, Moraes L, Santos CL, et al. Biphasic positive airway pressure minimizes biological impact on lung tissue in mild acute lung injury independent of etiology. Crit Care 2013;17(5):R228
61 Putensen C, Wrigge H. Clinical review: biphasic positive airway pressure and airway pressure release ventilation. Crit Care 2004; 8(6):492–497
62 Saddy F, Oliveira GP, Garcia CS, et al. Assisted ventilation modes reduce the expression of lung inflammatory and fibrogenic mediators in a model of mild acute lung injury. Intensive Care Med 2010;36(8):1417–1426
63 Beck J, Gottfried SB, Navalesi P, et al. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Respir Crit Care Med 2001;164(3):419–424
64 Dembinski R, Max M, Bensberg R, Rossaint R, Kuhlen R. Pressure support compared with controlled mechanical ventilation in experimental lung injury. Anesth Analg 2002;94(6):1570–-1576table of contents
65 Younes M, Webster K, Kun J, Roberts D, Masiowski B. A method for measuring passive elastance during proportional assist ventilation. Am J Respir Crit Care Med 2001;164(1):50–60
66 Younes M, Kun J, Masiowski B, Webster K, Roberts D. A method for noninvasive determination of inspiratory resistance during proportional assist ventilation. Am J Respir Crit Care Med 2001; 163(4):829–839
67 Alexopoulou C, Kondili E, Plataki M, Georgopoulos D. Patient-ventilator synchrony and sleep quality with proportional assist and pressure support ventilation. Intensive Care Med 2013;39(6):1040–1047
68 Chanques G, Kress JP, Pohlman A, et al. Impact of ventilator adjustment and sedation-analgesia practices on severe

asynchrony in patients ventilated in assist-control mode. Crit Care Med 2013;41(9):2177–2187
69 Spieth PM, Güldner A, Beda A, et al. Comparative effects of proportional assist and variable pressure support ventilation on lung function and damage in experimental lung injury. Crit Care Med 2012;40(9):2654–2661
70 Varelmann D, Wrigge H, Zinserling J, Muders T, Hering R, Putensen C. Proportional assist versus pressure support ventilation in patients with acute respiratory failure: cardiorespiratory responses to artificially increased ventilatory demand. Crit Care Med 2005;33(9):1968–1975
71 Spieth PM, Carvalho AR, Pelosi P, et al. Variable tidal volumes improve lung protective ventilation strategies in experimental lung injury. Am J Respir Crit Care Med 2009;179(8):684–693
72 Mutch WA, Harms S, Ruth Graham M, Kowalski SE, Girling LG, Lefevre GR. Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung. Am J Respir Crit Care Med 2000;162(1):319–323
73 Suki B, Alencar AM, Sujeer MK, et al. Life-support system benefits from noise. Nature 1998;393(6681):127–128
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
75 Gama de Abreu M, Spieth PM, Pelosi P, et al. Noisy pressure support ventilation: a pilot study on a new assisted ventilation mode in experimental lung injury. Crit Care Med 2008;36(3):818–827
76 Brack T, Jubran A, Tobin MJ. Dyspnea and decreased variability of breathing in patients with restrictive lung disease. Am J Respir Crit Care Med 2002;165(9):1260–1264
77 Spieth PM, Güldner A, Huhle R, et al. Short-term effects of noisy pressure support ventilation in patients with acute hypoxemic respiratory failure. Crit Care 2013;17(5):R261
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
79 Terzi N, Piquilloud L, Rozé H, et al. Clinical review: Update on neurally adjusted ventilatory assist - report of a round-table conference. Crit Care 2012;16(3):225
80 Allo JC, Beck JC, Brander L, Brunet F, Slutsky AS, Sinderby CA. Influence of neurally adjusted ventilatory assist and positive end-expiratory pressure on breathing pattern in rabbits with acute lung injury. Crit Care Med 2006;34(12):2997–3004
81 Brander L, Leong-Poi H, Beck J, et al. Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest 2009;135(3):695–703
82 Lecomte F, Brander L, Jalde F, et al. Physiological response to increasing levels of neurally adjusted ventilatory assist (NAVA). Respir Physiol Neurobiol 2009;166(2):117–124
83 Beck J, Campoccia F, Allo JC, et al. Improved synchrony and respiratory unloading by neurally adjusted ventilatory assist (NAVA) in lung-injured rabbits. Pediatr Res 2007;61(3):289–294
84 Sinderby C, Beck J, Spahija J, et al. Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest 2007;131(3):711–717
85 Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P. Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 2008;34(11):2010–2018
86 Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Crit Care Med 2012;40(5):1578–1585
87 Brander L, Sinderby C, Lecomte F, et al. Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. Intensive Care Med 2009;35(11):1979–1989