Pros and Cons of Assisted Mechanical Ventilation in Acute Lung Injury

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Introduction

Protective ventilation with low tidal volume (V_T) has become the standard of care in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) to prevent ventilator-associated lung injury (VALI) [1]. While tight control of V_T is more easily achieved with controlled ventilation, assisted ventilatory modes are available, and their performance and suitability for use in ALI/ARDS differs according to specific criteria. In the present chapter, we discuss the effects and applications of various assisted ventilation modes on different aspects of ALI/ARDS.

Modes of Assisted Ventilation

The major advantages and disadvantages of the most commonly used, promising or innovative modes of ventilator are summarized in **Table 1**. These modes are:

a) Volume assist-control ventilation
In volume assist-control ventilation a fixed V_T is delivered in time-cycled manner (independently from the patient) in response to inspiratory activity. Two limitations of this method are stacked breaths and a mismatch between the needed and the delivered V_T [2], which can be improved by proper setting of peak inspiratory flow [3].

Retrospective analyses of the ARMA trial [1] showed that low V_T during volume assist-control ventilation was not associated with increased need for sedation [4] or neuromuscular blocking agents (NMBAs) [5]. The combination of NMBAs and volume assist-control ventilation seems to be associated with improved oxygenation [6] and decreased lung inflammation [7] in ARDS. In ARDS patients with $PaO_2/FiO_2 < 120$ mmHg, the use of NMBAs in the first 48 hours of volume assist-control ventilation decreased mortality [8]. Nevertheless, the possibility of stacked breaths or patient/ventilator asynchrony in volume assist-control ventilation, resulting from mechanisms that have not been elucidated yet, suggests that this ventilation mode should be avoided in the first 48 hours of severe ARDS.

b) Pressure assist-control ventilation
As with volume assist-control ventilation, pressure assist-control ventilation can be triggered by both the patient's inspiratory effort and time cycling. However, in

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Table 1. Major advantages and disadvantages of the most commonly used, promising and innovative modes of assisted mechanical ventilation in acute lung injury/acute respiratory distress syndrome

Mode	VACV	PACV	PSV	BiPAP/APRV + SB	PAV/PPS	ASV	NAVA	Noisy PSV
Advantages	1) tight control of V_T settings 2) allows controlled ventilation 3) best clinically investigated mode	1) tight control of inspiratory Paw 2) allows controlled ventilation 3) decelerating flow profile 4) improves synchrony	1) tight control of inspiratory Paw 2) large clinical experience 3) improves lung function and inflammation	1) tight control of inspiratory Paw 2) allows non-supported breaths 3) improves lung function	1) adapts to the patient's demand 2) improves synchrony 3) improves comfort 4) increases variability of the respiratory pattern	1) control of inspiratory Paw 2) allows smooth transition from controlled to assisted ventilation 3) growing clinical experience	1) best synchrony 2) adapts to the patient's demand 3) increases variability of the respiratory pattern 4) reduces lung function and inflammation in experimental models	1) allows to increase the variability of the respiratory pattern independent of patient's own variability 2) decreases work of breathing 3) improves lung function and inflammation in experimental models
Disadvantages	1) potential for asynchrony 2) potential for stacked breaths 3) does not adapt to the patient's demand 4) may worsen lung function and inflammation in severe ARDS	1) no tight control of V_T 2) impact on lung function and inflammation not well known 3) does not adapt to the patient's demand	1) no tight control of V_T 2) only for assisted ventilation 3) does not adapt to the patient's demand	1) no tight control of V_T 2) increases work of breathing 3) potential for asynchrony	1) no tight control of V_T 2) only for assisted ventilation 3) potential for runaway	1) no tight control of V_T 2) physician has no control of relevant settings	1) no tight control of V_T (as part of the concept) 2) requires placement of an esophageal catheter and its proper position 3) only for assisted ventilation	1) no tight control of V_T (as part of the concept) 2) does not adapt to the patient's demand 3) no clinical data available

VACV: volume assist-control ventilation; PACV: pressure assist-control ventilation; PSV: pressure support ventilation; BiPAP/APRV+SB: biphasic intermittent positive airway pressure/airway pressure release ventilation with non-supported spontaneous breathing; PAV/PPS: proportional assist ventilation/proportional pressure support; ASV: adaptive support ventilation; NAVA: neurally-adjusted ventilatory assist; Noisy PSV: noisy pressure support ventilation; Paw: airway pressure

pressure assist-control ventilation, inspiratory flow is delivered at a variable rate and with a decelerating pattern. In addition, the resulting V_T depends strongly on the mechanical properties of the respiratory system and inspiratory effort. Thus, during pressure assist-control ventilation there is even less guarantee that V_T will be within the protective range. On the other hand, patient/ventilator synchrony during pressure assist-control ventilation may be improved and work of breathing reduced as compared to volume assist-control ventilation [9].

c) Pressure support ventilation

Pressure support ventilation (PSV) is the most common mode of assisted mechanical ventilation [10]. During PSV, each breath is supported by the same level of pressure at the airway (Paw). Pressure support can be triggered by either Paw or flow during inspiration. Cycling-off typically occurs at 25 % of peak flow. Patient-ventilator synchrony is improved with PSV, reducing the work of breathing and preventing fatigue of respiratory muscles. On the other hand, PSV depends on sufficient ventilatory drive and preserved mechanics of the respiratory system. As a consequence, V_T may exceed the limits of protective ventilation. In addition, typical cyclic-off settings of PSV are associated with proportionally shorter inspiration times, resulting in decreased mean Paw and possibly also in lung derecruitment. This limitation can be overcome by adjustments of cycling-off, pressure rise time, and positive end-expiratory pressure (PEEP).

d) Biphasic positive airway pressure/airway pressure release ventilation + supported/non-supported spontaneous breathing

In contrast to the previous modes, biphasic intermittent positive airway pressure and airway pressure release ventilation (BiPAP/APRV) allows free non-supported spontaneous breathing (SB) at two continuous positive airway pressure (CPAP) levels. Cycling between CPAP levels at pre-defined rates guarantees minimal alveolar ventilation. Between-cycle V_T depends on the mechanical properties of the respiratory system, cycling times and driving pressure itself (difference between CPAP levels), whereas V_T during spontaneous breathing depends on patient effort.

A major advantage of BiPAP/APRV+SB is a high mean Paw, which may be useful to stabilize alveoli in ALI/ARDS. Furthermore, inspiratory muscle activity non-supported by a positive Paw may promote lung recruitment, whereas intrathoracic pressures may decrease during free spontaneous breaths, facilitating venous return and improving cardiac filling [11]. Conversely, since inspiratory effort can occur at any moment during cycling, spontaneous breathing during the change from lower to higher CPAP may increase V_T above the protective range. Moreover, it is currently not known how much spontaneous breathing activity should be used during BiPAP/APRV+SB. Although in clinical studies spontaneous breathing was responsible for 10 – 20 % of total minute ventilation, animal studies have reported values as high as 60 %. Thus, the most suitable settings for BiPAP/APRV+SB in patients with ALI/ARDS remain to be determined.

e) Proportional assist ventilation/proportional pressure support

Proportional assist ventilation/proportional pressure support (PAV/PPS) generates positive pressure throughout inspiration in proportion to patient-generated flow and volume – in other words, the ventilator is able to adapt to changes in the patient's ventilatory demand. Despite this advantage, PAV/PPS is rarely used. This

is due in part to the need for online measurements of elastance and resistance of the respiratory system to optimize the settings of flow and volume assist components. More recently, a modification of PAV (PAV+) has been proposed to overcome this limitation. In PAV+, the mechanical properties of the respiratory system are assessed automatically during periodic occlusions of the mechanical ventilator at end-inspiration, when inspiratory muscle activity declines to zero [12].

Although patient/ventilator synchrony seems to be improved in PAV, V_T may be outside the protective range, even in the absence of runaway. The reduction in flow and volume assistance that could theoretically resolve this limitation would probably increase the work of breathing.

V

f) Adaptive support ventilation

Adaptive support ventilation (ASV) is a closed loop mode that adapts respiratory rates and V_T based on the Otis least work of breathing formula. After defining the desired minute ventilation, the ventilator iteratively adjusts the respiratory rate and V_T based on estimation of expiratory resistance and compliance of the respiratory system, at the lowest possible Paw. One particular advantage of ASV is that it can be used for both controlled and assisted ventilation (dual-mode), with smooth transition to the weaning period. If the spontaneous respiratory rate is not high enough during weaning, mandatory cycles are generated.

Although different respiratory rates and V_T are possible during ASV, a 'safety window' limits V_T ranges to avoid non-protective ventilation in ALI/ARDS. In a physical lung model with varying mechanical properties, ASV successfully avoided peak Paw > 28 cmH_2O compared to conventional protective ventilation [13]. However, V_T generated by ASV for the ideal body weight (IBW) seems to be slightly higher than 8 ml/kg during an open lung approach in patients with ALI [14]. These findings suggest that in patients with ALI/ARDS and fairly preserved respiratory system mechanics, ASV could lead to V_T higher than 6 ml/kg.

g) Neurally-adjusted ventilatory assist

In this innovative approach, the mechanical ventilator is not triggered or cycled-off by Paw or inspiratory flow. Neurally-adjusted ventilatory assist (NAVA) uses the electrical activity of the diaphragm (EAdi) as an indicator of respiratory drive to guide ventilatory support. This seems to be advantageous in terms of patient-ventilator synchrony.

Theoretically, V_T during NAVA could exceed the protective range, since volumes are solely driven by inspiratory drive and a gain factor is used to convert electrical diaphragmatic activity into pressure support. Nevertheless, relatively low V_T has been reported during NAVA [15]. These findings suggest that central respiratory drive and electrical diaphragmatic activity both adapt to prevent high V_T in ALI/ARDS. However, V_T during NAVA is not always determined by diaphragmatic activity – it may also be influenced by airway flow. Thus, if intercostal muscle movement precedes diaphragmatic electrical activity, NAVA applies a fixed pressure support to the airways, working as PSV.

h) Noisy pressure support ventilation

The respiratory system may benefit from breath-by-breath variations in Paw [16]. In contrast to controlled mechanical ventilation, most of the assisted ventilation modes support such variability.

Noisy PSV has an advantage over other assisted ventilation modes such as PAV and NAVA. During PSV, breath-by-breath differences in inspiratory effort and inspiratory time may generate oscillations in V_T and respiratory rate, but these are mostly reduced when compared to normal spontaneous breathing [17]. In contrast, PAV [17] and NAVA [18] may result in higher variabillity of the respiratory pattern than PSV. However, the variability of the respiratory pattern depends on the intrinsic variability of the patient, and is therefore influenced by sedation and disease. Noisy PSV is able to overcome such limitations by allowing pressure support to vary breath by breath as triggered by the patient, even if the respiratory center and muscles are not able to generate enough variability [19].

V_T values in noisy PSV can reach below or above the recommended limits, depending on the intrinsic inspiratory drive, mechanical properties of the respiratory system, and the level of variability chosen.

Effects on Gas Exchange

Most of the assisted ventilation modes described in this chapter have been reported to improve oxygenation compared to controlled mechanical ventilation in experimental ALI/ARDS. Our group [19] found that PSV improved oxygenation and reduced intrapulmonary shunt compared to controlled ventilation in a model of ALI/ARDS. In contrast, clinical studies have reported conflicting results concerning the effects of PSV on gas exchange. Cereda et al. [20] found that controlled ventilation and PSV led to comparable PaO_2 in patients with ALI. Yoshida et al. [21] documented improved oxygenation when patients with ARDS were switched from controlled ventilation to PSV. Differences in the severity or phase of respiratory failure may explain these conflicting findings.

The beneficial effects of BiPAP/APRV+SB on PaO_2 and intrapulmonary shunt have been well documented in oleic acid-induced respiratory failure [22]. Furthermore, BiPAP/APRV+SB seems to improve gas exchange more than PSV [23]. Our group observed similar improvements in oxygenation during BiPAP/APRV+SB compared to controlled ventilation, but not PSV, in other models of ALI/ARDS [19]. Clinical trials confirm that BiPAP/APRV+SB improves oxygenation compared to controlled ventilation [23, 24]. One recent study suggests that this mode results in even higher PaO_2 and lower intrapulmonary shunt than PSV in ARDS [21].

In a mixed population of patients with respiratory failure resulting from obstructive as well as restrictive lung disease, PAV was not superior to PSV in terms of gas exchange [25]. It should be noted that studies on the effects of PAV and ASV on gas exchange in ALI/ARDS are lacking.

In a rodent model of ALI/ARDS, NAVA resulted in improved oxygenation compared to controlled ventilation [26]. However, V_T values were not matched, resulting in increased lung injury in the controlled ventilation group. To our knowledge, there are no clinical studies comparing the effects of NAVA and controlled ventilation on gas exchange in ALI/ARDS.

An experimental pilot study from our group suggested that noisy PSV might improve oxygenation and reduce intrapulmonary shunt compared to controlled ventilation in ALI/ARDS induced by saline lung lavage [19]. However, V_T differed between the groups. Furthermore, oxygenation during noisy PSV was higher than during PSV and BiPAP/APRV+SB. Interestingly, the level of variability seems to play an important role in noisy PSV. Maximal improvement in PaO_2 is achieved

when the resulting coefficient of variation of V_T is between 20 – 30 %, i.e., similar to spontaneous breathing in healthy subjects [27]. However, there are no clinical data on noisy PSV in ALI/ARDS.

Effects on the Regional Distribution of Lung Aeration

Spontaneous breathing not supported by pressure is able to increase lung gas volumes during mechanical ventilation with BiPAP/APRV in experimental lung injury [28]. In oleic acid-induced ALI/ARDS, the amount of non-aerated (-100 to 0 Hounsfield Units, HU) and poorly aerated (-500 to -100 HU) lung tissue in the most caudal lung zones decreases during BiPAP/APRV+SB, suggesting that diaphragmatic muscle activity is an effective means for reversing atelectasis in those areas. Such alveolar recruitment seems to be associated with a more even distribution of aeration and less hyperinflated (-1000 to -900 HU) lung tissue [28]. In addition, BiPAP/APRV+SB is more effective for increasing lung aeration at end-expiration compared to PSV [29]. Recently, a clinical study has confirmed that BiPAP/APRV+SB and PSV both increase lung aeration in patients with ALI/ARDS in relation to controlled ventilation [21].

The potential of BiPAP/APRV+SB to reduce cyclic changes in lung aeration is illustrated in **Figure 1**. In addition to the potential of BiPAP/APRV+SB for lung

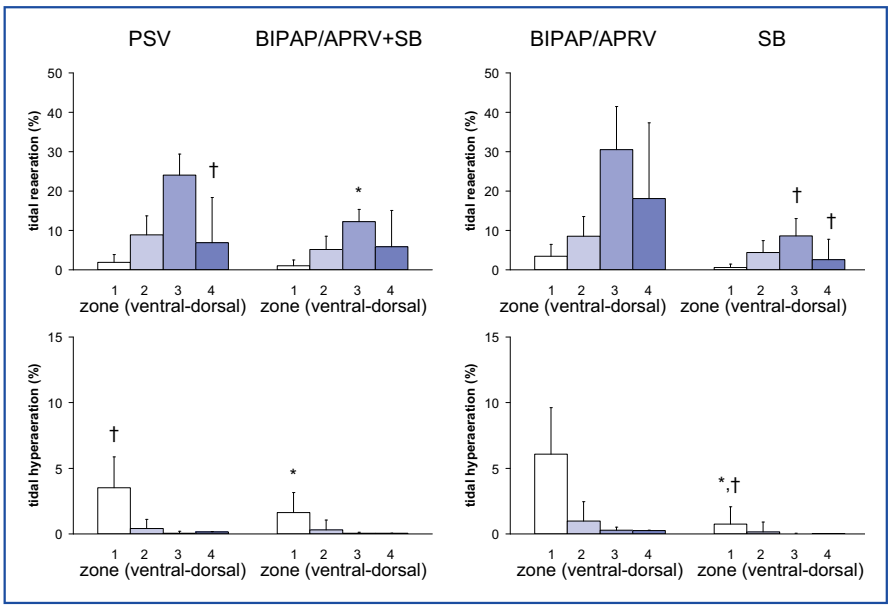

Fig. 1. Tidal reaeration and hyperaeration during pressure support ventilation (PSV), biphasic positive pressure ventilation/airway pressure release ventilation+ spontaneous breaths (BIPAP/APRV+SB), controlled (BIPAP/APRV) and spontaneous (SB) breath cycles in experimental acute lung injury. Calculations were performed for different lung zones from ventral to dorsal (1-ventral, 2-mid-ventral, 3-mid-dorsal and 4-dorsal) at lung base using dynamic computed tomography. Bars and vertical lines represent means and standard deviations, respectively. *, $p < 0.05$ *vs.* PSV; †, $p < 0.05$ vs. BIPAP/APRV (controlled ventilation). Adapted from [29] with permission.

recruitment, lower V_T during spontaneous breaths seem to be an important co-determinant of reduced tidal reaeration and hyperaeration in dynamic computed tomography (CT) scans in this mode.

Effects on the Regional Distribution of Lung Ventilation

In assisted ventilation, changes in the regional distribution of ventilation normally follow changes in aeration. Using dynamic CT scanning, our group did not detect a ventilation shift to more caudal lung regions during PSV compared to controlled ventilation [29] in experimental lung injury. Accordingly, in patients with ALI/ARDS, PSV did not improve ventilation/perfusion matching as compared to pressure controlled ventilation [23]. Using the technique of vibration response imaging, Dellinger et al. [30] were able to show that pressure support of spontaneous breathing was not associated with increased acoustic energy in more caudal lung regions as compared to pressure control ventilation.

A shift of ventilation during BiPAP/APRV+SB from non-dependent towards dependent lung zones has been reported in pigs with ALI/ARDS [28, 31]. Using the MIGET technique, an improvement in global ventilation/perfusion matching was detected during BiPAP/APRV+SB compared to controlled ventilation in patients with ALI/ARDS in the supine position [23], suggesting that ventilation was redistributed to dorsal areas. However, using dynamic CT analysis, we were not able to show that BIPAP/APRV+SB shifted the distribution of ventilation compared to PSV in experimental ALI/ARDS [29].

Effects on Regional Distribution of Lung Perfusion

It is a common belief that improved oxygenation following assisted ventilation reflects lung recruitment with increased perfusion of dependent regions.

In experimental models of ALI/ARDS, assisted ventilation with BiPAP/APRV+SB seems to result in increased perfusion of dependent lung zones compared to controlled ventilation [31]. Nevertheless, local ventilation/perfusion matching was not significantly increased in dorsal areas during BiPAP/APRV+SB compared to controlled ventilation [31], suggesting that oxygenation is strongly dependent on regional aeration.

In fact, recent works from our group have shown that increased oxygenation during PSV and noisy PSV compared to controlled ventilation is mediated by a shift of perfusion from dependent towards non-dependent lung zones [19, 32]. Accordingly, reduced regional aeration and alveolar derecruitment were observed in those areas (**Fig. 2**). Possibly, when hypoxic pulmonary vasoconstriction is preserved, a lower mean airway and transpulmonary pressure during PSV and noisy PSV may further contribute to the redistribution of perfusion by decreasing capillary impedance of better-aerated, non-dependent zones. Such a mechanism was likely involved in the improvement in oxygenation observed in patients with ALI/ARDS during PSV compared to controlled ventilation [21].

It seems that assisted ventilation has the potential to recruit the lungs if enough transpulmonary pressure is generated in dependent lung zones, and also to divert perfusion towards better aerated lung areas if recruitment does not occur.

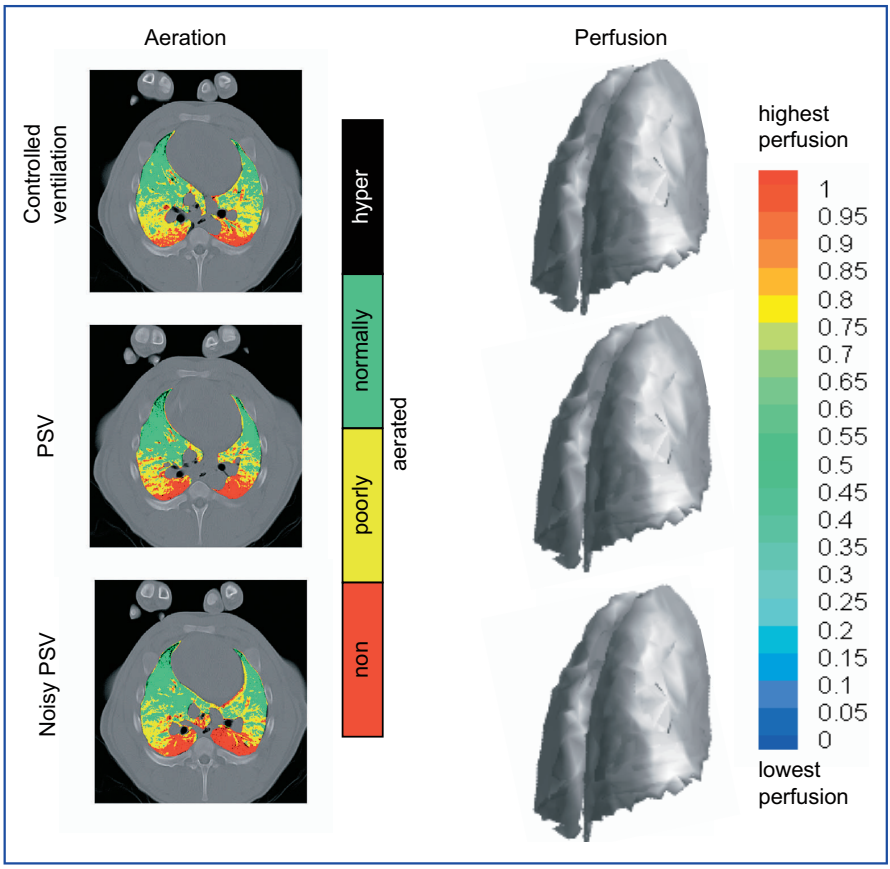

Fig. 2. Color maps of aeration on computed tomography (CT) scans of chest at hilum (left column) and of regional perfusion in whole lungs (right column) in a pig with acute lung injury induced by saline lavage. Measurements were performed during controlled ventilation as well as assisted pressure support ventilation (PSV) and noisy PSV in the same animal. The lung surface extracted from CT analysis is shown to facilitate the visualization of the spatial distribution of perfusion in the lungs. Arterial oxygenation improved during PSV and noisy PSV compared to controlled ventilation due to redistribution of perfusion towards better aerated regions rather than increased lung aeration. Adapted from [19] with permission.

Ventilator-associated Lung Injury

Mechanical ventilation may initiate or exacerbate lung injury as a result of stress and/or strain [33], opening and closing of collapsed peripheral airways and/or atelectatic lung regions, mainly located in dependent lung regions, or redistribution of pulmonary perfusion [34]. These mechanisms involve physical disruption of the lung and promote cell and inflammatory-mediator-induced injury. Inflammatory-mediator induced injury is particularly relevant because of possible systemic sequels such as multiple system organ failure, the primary cause of death in ALI/ARDS.

Assisted mechanical ventilation has been suggested to minimize the development of VALI by increasing lung volume and reducing atelectasis, leading to

improvement in lung elastance, with consequent reduction in transpulmonary pressure and in the amount of opening and closing of peripheral airways and atelectasis. Moreover, pleural pressures are redistributed. On the other hand, spontaneous breathing during assisted mechanical ventilation may exacerbate lung injury by increasing patient-ventilator asynchrony and rapid shallow breathing, and inducing further atelectasis and tidal recruitment–derecruitment [35]. Additionally, negative pleural pressures may increase intrathoracic blood volume, worsening pulmonary edema and lung damage [36].

Transpulmonary pressure is the difference between the pressure inside the alveoli (Palv) and pleural pressure (Ppl). Ppl plays a relevant role, since it influences factors that promote VALI, as mentioned above. However, there are major differences between the effects of Palv and Ppl in controlled and assisted mechanical ventilation (**Fig. 3**). During controlled mechanical ventilation, Ppl depends on V_T and lung elastance. The resulting Palv depends on V_T and the elastances of the lung and chest wall. In case of normal or quasi normal chest wall elastance, Ppl is easily predictable from Palv and V_T delivered. Increasing V_T increases Ppl and Palv accordingly. In cases of altered chest wall elastance, for the same delivered V_T, Palv may be substantially higher for unchanged Ppl. However, even in this case, if Palv is maintained within usually recommended safe limits (28 to 30 cmH_2O), the consequent Ppl might be lower, but not higher, than expected.

In contrast, during assisted mechanical ventilation, Palv does not necessarily reflect Ppl, since the degree of activation of respiratory muscles and consequent reduction in Ppl must be taken into account. In other words, even with constant Palv, the increase in inspiratory effort and Ppl, determines higher transpulmonary pressure. This has some clinical implications: a) Direct evaluation can be made based on the estimation of inspiratory effort by means of the P0.1, muscular pressure (for example, during PAV), or measurement of diaphragmatic activity (during NAVA); b) since Paw, which roughly represents Palv, does not provide any useful and reliable information about the real transpulmonary pressure, it should be carefully interpreted in the setting of minimally injurious ventilatory parame-

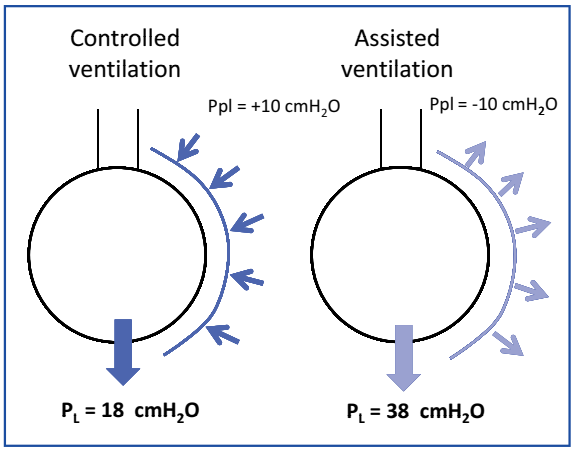

Fig. 3. Schematic representation of possible pressures applied to two alveoli during controlled (left alveolus) and assisted (right alveolus) mechanical ventilation. The pressure applied to the visceral pleura corresponds to the distending force of the lung per unit area. This is the transpulmonary pressure (P_L), which is the difference between the pressure inside the alveoli (Palv) and pleural pressure (Ppl). For the situation presented, readings of airway pressure (≈ Palv) are near the protective value of 28 cmH_2O during both controlled and assisted ventilation. However, P_L is only 18 cmH_2O during controlled ventilation, and as high as 38 cmH_2O during assisted ventilation.

ters. When assisted mechanical ventilation is associated with minimal inspiratory effort, Palv becomes a more reliable indicator of the real transpulmonary pressure; c) since ineffective breathing and higher transpulmonary pressure may occur during assisted mechanical ventilation, they should be carefully monitored.

Few experimental studies have evaluated the effects of assisted mechanical ventilation on VALI. Saddy et al. [37] compared the effects of different assisted ventilation modes (pressure assist-control ventilation with inspiratory:expiratory ratio [I:E] = 1:2 and 1:1, and Bi-Vent, a variant of BiPAP that allows spontaneous breaths assisted by pressure support in both the lower and the higher Paw levels) with pressure control ventilation on lung histology, arterial blood gases, inflammatory and fibrogenic mediators in experimental ALI in rats. Interestingly, the tidal volume delivered and the inspiratory effort were higher during assisted mechanical ventilation modes. However, inspiratory effort estimated by P0.1 was lower with Bi-Vent and PSV, and higher during assisted-pressure control modes. The main findings were that assisted ventilation modes had more beneficial effects on respiratory function and reduced lung injury compared to PSV. Among assisted ventilation modes, Bi-Vent and PSV had better functional results with less lung damage and expression of inflammatory mediators. This study raised interesting questions for assisted mechanical ventilation: a) V_T, within certain limits, and increased transpulmonary pressure may not be specific determinants of VALI; b) higher inspiratory effort during assisted mechanical ventilation could increase injury, and the 'safe' level of inspiratory effort should be determined in the near future; c) P0.1 could be useful to optimize assisted ventilation by achieving optimal recruitment with minimal stress and strain; d) modalities of assisted ventilation that favor lower I:E ratio may lead to less hyperinflation. Interestingly, Bi-Vent and PSV were associated with lower hyperinflation compared to pressure assist-control ventilation 1:1, which could be due to a better animal-ventilator interaction that reduced respiratory drive with consequent decrease in the inspiratory transpulmonary pressure.

In line with these data, Gama de Abreu et al. [29], showed that reduced tidal re-aeration and hyperaeration during BiPAP/APRV+SB compared to PSV did not result from a decrease in non-aerated areas at end-expiration or different distribution of ventilation, but rather from lower mean V_T. This suggests that the ratio between spontaneous and controlled breaths plays a pivotal role in reducing tidal re-aeration and hyperaeration during BIPAP/APRV+SB.

Different factors may promote reduced lung injury during assisted ventilation: a) recruitment of dependent atelectatic lung regions, reducing opening and closing during tidal breath, thus limiting shear stress forces; b) more homogeneous distribution of regional transpulmonary pressures; c) variability of breathing pattern; d) redistribution of perfusion towards non-atelectatic injured areas [19]; and e) improved lymphatic drainage.

In another experimental study, Brander et al. [26] found that NAVA was as effective as protective ventilation in preventing VALI, attenuating excessive systemic and remote organ inflammation, and preserving cardiac and kidney function in rabbits. However, in that study, the V_T delivered by NAVA was substantially lower that that delivered during a protective ventilation strategy (3 vs. 6 ml/kg).

Our group has recently shown that in saline lung lavage, protective ventilation with PSV and noisy PSV was associated with reduced histological lung damage and reduction in interleukin (IL)-6 in the lung tissue as compared to protective

controlled mechanical ventilation [38]. However, other authors found that BiPAP/APRV+SB did not improve hemodynamic and respiratory function, causing greater histopathologic damage to the lungs in a model of intra-abdominal hypertension [39]. In contrast with most experimental findings, Forel et al. [7] showed that NMBAs reduced pulmonary and systemic inflammation in patients with ARDS ventilated with a lung-protective strategy in volume assist-control ventilation. More recently, the same group reported a decrease in mortality in severe ARDS (PaO_2/FiO_2 < 120 mmHg) with the use of NMBAs [8].

Taken together, these observations suggest that the type of assisted mechanical ventilation and the amount of inspiratory effort play a relevant role in VALI, especially in more severe ARDS patients. In patients with abdominal compartment syndrome, assisted mechanical ventilations should be used cautiously or avoided.

Patient-ventilator Asynchrony

Patient-ventilator asynchrony refers to the uncoupling between the mechanically delivered breath and the patient's respiratory effort. It is common during assisted mechanical ventilation and may affect the morbidity of critically ill patients. Close inspection of pressure, volume and flow waveforms – displayed by modern ventilators – may help the physician to recognize and act appropriately to minimize patient-ventilator asynchrony.

A large prospective study reported that one-fourth of critically ill patients exhibited a high incidence of asynchrony during assisted ventilation. Such a high incidence was associated with prolonged duration of mechanical ventilation. Patients with frequent ineffective triggering may receive excessive levels of ventilatory support [35]. It has been shown that in patients with ARDS and increased breathing effort receiving small V_Ts, pressure-targeted compared to volume assist controlled ventilation may provide more comfort by decreasing respiratory drive during the triggering phase [40].

During PSV, markedly reducing the level of support or inspiratory duration to reach a V_T of about 6 ml/kg eliminated ineffective triggering in two-thirds of critically ill patients with weaning difficulties and a high percentage of ineffective efforts without inducing excessive work of breathing or modifying patient respiratory rate [41]. Furthermore, different studies have shown that optimization of pressure rise time and/or inspiratory/expiratory triggering is mandatory to avoid patient ventilator asynchronies in patients with ALI [42].

Sigh during Assisted Mechanical Ventilation

Assisted mechanical ventilation, especially pressure limited modalities, might promote progressive derecruitment when mean airway pressure is not optimized. For this reason, periodic hyperinflations (sighs) might be useful to prevent progressive reduction in lung volume and atelectasis. Sighs have been shown to improve recruitment and gas-exchange in ALI/ARDS patients during controlled mechanical ventilation [43]. Sighs during PSV in patients with early ARDS have been proposed to improve gas exchange and lung volume and decrease the respiratory drive [44]. In a paraquat-induced ALI model, Steimback et al. [45] showed that a reduction in sigh frequency of up to 10 sighs per hour had a protective

effect on lung and distal organs. No clinical data are currently available about the effects of sighs during assisted ventilation in ALI/ARDS.

Ventilator-induced Diaphragmatic Dysfunction

Controlled mechanical ventilation is an important cause of diaphragmatic weakness, associated with a syndrome known as ventilator-induced diaphragmatic dysfunction [46]. Clinical studies report that the duration of mechanical ventilation is associated with a decline in diaphragmatic force. It is unclear whether this relation is causal or influenced by other confounders [47]. Animal studies have demonstrated that ventilator-induced diaphragmatic dysfunction is minimized with the use of partial support modes of mechanical ventilation [48, 49]. A recent study found that healthy piglets ventilated for 72 h with adaptive support ventilation (ASV) presented greater phrenic nerve-stimulated diaphragmatic strength and fewer histological signs of atrophy compared to those ventilated with controlled mechanical ventilation [50]. Therefore, it seems important to allow as much diaphragmatic activity as possible. However, further studies are required to ascertain the optimal level of diaphragmatic effort and to determine whether the specific method of promoting diaphragmatic effort during mechanical ventilation (e.g., spontaneous breathing trials, assist-control, pressure-support, newer modes such as NAVA, etc.) has any impact on the risk of ventilator-induced diaphragmatic dysfunction. In addition, persistent oxidative stress [49] and substantial residual deficit of diaphragmatic force have been associated with partial support modes of mechanical ventilation or intermittent periods of spontaneous breathing, even in the absence of atrophy [48]. These findings suggest that other measures designed to target the specific cellular pathways involved in muscle injury may be required in order to prevent or reverse ventilator-induced diaphragmatic dysfunction.

Conclusion

The use of assisted mechanical ventilation in ALI/ARDS improves oxygenation, decreases the need for sedation and vasoactive drugs, and preserves the force of contraction and structure of respiratory muscles. Assisted ventilation modes that allow no or less supported spontaneous breathing require increased muscle respiratory activity and are more likely to recruit the lungs compared to modes that support individual breaths. In experimental ALI/ARDS, breath supported ventilation improves oxygenation by redistribution of perfusion to better aerated lung zones, rather than recruitment.

Even though assisted ventilation has been shown not to affect or decrease VALI in animal models of ALI/ARDS, recent evidence suggests that in the first 48 hours of severe ARDS ($PaO_2/FiO_2 < 120$ mmHg) the use of controlled ventilation combined with NMBAs helps to preserve lung function and reduce mortality, when compared to a ventilatory strategy in which the patient triggers the mechanical ventilator to get a predefined fixed V_T. Thus, spontaneous breathing activity should be avoided in such patients during ventilation with volume assist-control ventilation in the early phase of severe ARDS. Whether such restriction also applies to other forms of assisted ventilation that allow better patient-ventilator synchrony and how these modes compare to each other is still unclear.

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