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Lung Protective Ventilation in Brain-Injured Patients: Low Tidal Volumes or Airway Pressure Release Ventilation?

Ravi Garg[1]

[1]Division of Neurocritical Care, Department of Neurology, Loyola University Medical Center, Maywood, Illinois, United States

Address for correspondence Ravi Garg, MD, Division of Neurocritical Care, Department of Neurology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, United States (e-mail: ravigarg@lumc.edu).

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Abstract

The optimal mode of mechanical ventilation for lung protection is unknown in brain-injured patients as this population is excluded from large studies of lung protective mechanical ventilation. Survey results suggest that low tidal volume (LTV) ventilation is the favored mode likely due to the success of LTV in other patient populations. Airway pressure release ventilation (APRV) is an alternative mode of mechanical ventilation that may offer several benefits over LTV in this patient population. APRV is an inverse-ratio, pressure-controlled mode of mechanical ventilation that utilizes a higher mean airway pressure compared with LTV. This narrative review compares both modes of mechanical ventilation and their consequences in brain-injured patients. Fears that APRV may raise intracranial pressure by virtue of a higher mean airway pressure are not substantiated by the available evidence. Primarily by virtue of spontaneous breathing, APRV often results in improvement in systemic hemodynamics and thereby improvement in cerebral perfusion pressure. Compared with LTV, sedation requirements are lessened by APRV allowing for more accurate neuromonitoring. APRV also uses an open loop system supporting clearance of secretions throughout the respiratory cycle. Additionally, APRV avoids hypercapnic acidosis and oxygen toxicity that may be especially deleterious to the injured brain. Although high-level evidence is lacking that one mode of mechanical ventilation is superior to another in brain-injured patients, several aspects of APRV make it an appealing mode for select brain-injured patients.

Keywords
- ► pressure-controlled inverse ratio
- ► airway pressure release ventilation
- ► biphasic positive airway pressure
- ► intracranial pressure
- ► cerebral hemodynamics

Introduction

Randomized controlled trials (RCT) of lung protective modes of ventilation have excluded patients with elevated intracranial pressure (ICP),[1,2] leaving uncertainty to which mode is superior in brain-injured patients. A recent international survey of intensivists caring for patients with severe traumatic brain injury suggested that low tidal volume (LTV) ventilation is the favored ventilator strategy.[3]

LTV ventilation refers to a volume-assist-control mode of mechanical ventilation in which tidal volumes are set to 6 mL/kg of predicted body weight with an absolute plateau pressure ceiling of 30 cm of H_2O popularized by a landmark RCT.[1] Airway pressure release ventilation (APRV) is a pressure-limited, time-cycled, assisted mode of mechanical ventilation that allows unrestricted spontaneous breathing independent of ventilator cycling. This is achieved using an active expiratory valve. A high pressure (P_{high}), low pressure (P_{low}), high

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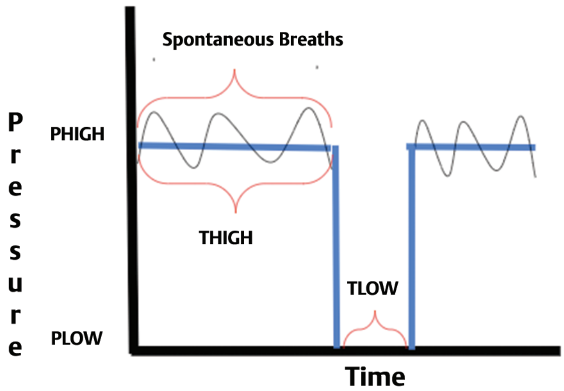

Fig. 1 Pressure-time schematic for airway pressure release ventilation. P_{high} refers to the continuous positive airway pressure; P_{low} is the set pressure after the P_{high} is released; T_{high} is the time of the respiratory cycle spent delivering P_{high}; and T_{low} is the time of the respiratory spent delivering P_{low}. Spontaneous breathing may occur throughout the respiratory cycle. P_{high}, high pressure; P_{low}, low pressure; T_{high}, high time; $T_{low,}$ low time.

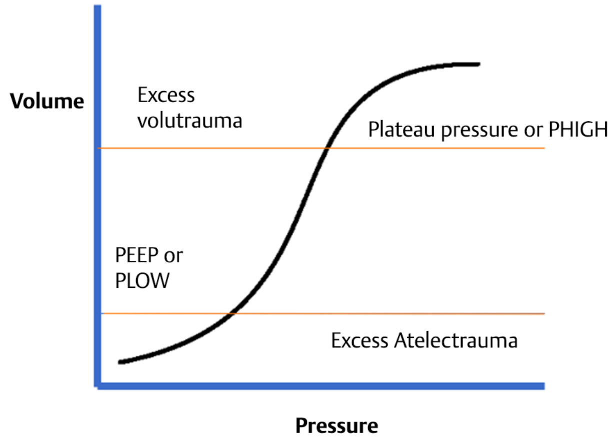

Fig. 2 Volume-pressure inspiratory curve**.** Lung protective ventilation occurs in a range to avoid excess atelectrauma and volutrauma. The area below the lower inflection point is the zone of excess atelectrauma; and the corresponding pressure is targeted depending on the mode of mechanical ventilation. Similarly, the area above the upper inflection point is the zone of excess volutrauma; and the corresponding pressure is targeted depending on the mode of mechanical ventilation. In low tidal volume ventilation, a tidal volume is set based on ideal body weight and the corresponding plateau pressure occurring with the volume has a ceiling. Of note, spontaneous breathing that occurs during airway pressure release is not referable to this figure. P_{high}, high pressure; P_{low}, low pressure; PEEP, positive end-expiratory pressure.

time (T_{high}), low time (T_{low}), and fraction of inspired oxygen (FiO_2) are the parameters set in APRV (►**Fig. 1**). The P_{high} is the continuous positive airway pressure delivered by the ventilator that is interrupted by a release of the P_{high} to the P_{low}. The P_{high} is set at the desired plateau pressure and P_{low} is set at 0 or 5 mm Hg. The T_{high} is the time spent delivering the P_{high} and the T_{low} is the time spent delivering the $P_{low.}$ The times are set such that 80 to 90% of the cycle time is spent at the P_{high}; and typical settings include a T_{high} of 4 to 6 seconds and a T_{low} of 0.2 to 0.8 seconds.[4] Low time (T_{low}) may be optimally set by visualizing the flow-time scalar such that expiratory flow termination occurs at 75% of the peak expiratory flow rate. This results in minimal variation in alveolar volume between end-inspiration and the release phase. Additionally, unrestricted spontaneous breathing occurs throughout the respiratory cycle.

The similarities between the lung protective goals of LTV and APRV may be appreciated graphically from a volume-pressure inspiratory curve (►**Fig. 2**). Both modes of mechanical ventilation seek to ventilate patients within a range that maximizes alveolar recruitment and prevents alveolar distention. In patients with additional oxygenation needs, the positive end-expiratory pressure (PEEP) or FiO_2 may be increased in LTV, while the P_{high} and T_{high} may be increased in APRV. A theoretical advantage of APRV is utilization of a higher mean airway pressure by virtue of continuous positive airway pressure to restore functional residual capacity and begin inspiration at a more favorable (compliant) portion of volume-pressure inspiratory curve.

Several aspects of APRV may make it a promising alternative to LTV in brain-injured patients.

Lung Protective Ventilation on Cerebral Hemodynamics

Gradual uptitration of PEEP has been suggested as first-line therapy for the management of refractory hypoxemia in patients managed with an LTV strategy.[5] The relationship between PEEP and ICP is complex. The mechanisms by which PEEP change ICP are multifactorial, but are primarily due to effects of increased thoracic pressure. Increased thoracic pressure may be directly transmitted to the cranium; and may also increase jugular venous pressure causing subsequent cerebral venous congestion. This is coupled with a decreased venous return and cardiac output. The combination results in impaired cerebral perfusion pressure (CPP).

The effects of PEEP on ICP may be influenced by ventricular and pulmonary compliance; those with normal pulmonary and ventricular compliance may have the ability to buffer against changes in ICP in response to changes in vascular pressure and venous outflow.[6] Those patients with abnormal pulmonary and cerebral ventricular compliance may be especially susceptible to increased ICP related to changes in PEEP. In the largest study to date exploring the relationship between PEEP and ICP, there was a statistically significant relationship between PEEP and both ICP and CPP in the group of patients with severe lung injury; and this supports the PEEP sensitivity hypothesis in patients with both poor pulmonary and cerebral ventricular compliance.[7] Of note, the increase in ICP noted by the authors was small: a 1 cm H_2O increase in PEEP would potentially increase ICP by 0.31 mm Hg in patients with severe lung injury.

Compared with LTV, ventilation with APRV is achieved using a higher mean airway pressure. A theoretical concern of APRV is CPP may be compromised by both increased ICP and reduction in mean arterial pressure due to increased intrathoracic pressure. These theoretical concerns are not substantiated by the available clinical data. In fact, the opposite effects

Table 1 Effects of higher mean airway pressure due to inverse ratio ventilation on cerebral hemodynamics

Article Year	Study type	Number of patients/ Intracranial Pathology	Effect on MAP	Effect on ICP (mm Hg)	Effect on CPP (mm Hg)	Effect on $PaCO_2$ or $EtCO_2$ (mm Hg)	Effect on PaO_2 (mm Hg)
Clarke[8] 1997	Prospective observational	9/Traumatic brain injury	No change	No change	No change	Mean decrease (1.8)	Not reported
Fletcher et al[29] 2018	Retrospective	21/Traumatic brain injury	Not reported	Mean decrease (2.9)	No change	No change	Mean increase (36.3)
Edgerton et al[30] 2019	Retrospective	15/Traumatic brain injury	No change	No change	No change	No change	Mean increase (37.9)
Montanaro[31] 2016	Case report	1/Traumatic brain injury	Not reported	Decrease[a]	Not reported	Not reported	Not reported
Marik et al[9] 2012	Case report	1/Subarachnoid hemorrhage	Decrease (3)	Increase (1)	Decrease (4)	Decrease (9)	Increase (56)

Abbreviations: CPP, cerebral perfusion pressure; $EtCO_2$, end-tidal carbon dioxide; ICP, intracranial pressure; MAP, mean arterial pressure; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen;

[a]Precise value not reported. Search strategy noted in ► **Supplementary Appendix A** (available in the online version).

on cerebral hemodynamics may occur (►**Table 1**). The effects of elevated intrathoracic pressure may be offset by a greater efficiency in gas exchange; and a greater reduction in partial pressure of carbon dioxide.[8] Marik et al noted a 1 mm Hg increase in ICP and 4 mm Hg decrease in CPP.[9] Despite these changes, both values remained within acceptable ranges: 3 and 70 mm Hg, respectively. They also noted a corresponding increase in cerebral blood flow after initiating APRV as measured by carotid Doppler. They hypothesized that initiation of APRV improved oxygenation and decreased V/Q mismatching that resulted in less pulmonary arterial vasoconstriction. This subsequently may have improved right ventricular function and cardiac output. Therefore, both modes are likely safe from an ICP standpoint.

A benefit of APRV over LTV is improvement in systemic hemodynamics and by virtue cerebral hemodynamics. Hemodynamic improvements are a function of spontaneous breathing[4,10-13] during APRV. In patients ventilated with APRV, spontaneous breathing causes a physiological decrease in pleural pressure and increase in abdominal pressure; and these both promote an increase in preload and a subsequent increase in cardiac output.[4,13] This finding is supported by a meta-analysis of clinical trials.[14] In certain patients, such as those with ICP crises or who require hemodynamic augmentation during vasospasm, hemodynamic improvement by virtue of mechanical ventilation would be welcome.

Limited Sedation Use with APRV

Another aspect of APRV that may be favored in patients with cerebral injury is the reduced use of sedation compared with LTV.[12,15] Although sedation promotes patient-ventilator synchrony, there may deleterious consequences to excess sedation in brain-injured patients.

The higher levels of sedation used with LTV are likely a reflection of a mismatch between central respiratory drive and maximum minute ventilation provided by LTV. Importantly, central respiratory drive may be abnormally high in patients with cerebral injury. Sedation may impair accurate neuromonitoring and depress the normal cough reflex.[4] APRV uses an open breathing system and secretions may be easily cleared throughout the respiratory cycle. In a conventional closed looped system coughing may lead to double-triggering of the ventilator and promote increased sedation use.

During APRV, unrestricted breathing allows the patient to control their respiratory pattern, no matter how irregular, without an arbitrary preset inspiratory: expiratory (I:E) ratio. This is consistent with data primarily from other patient types that has found APRV decreases the need for neuromuscular blockade use by 70%.[16] Of note, this strategy is less effective with additional fixed pressure support above P_{high}, as the patient's intrinsic respiratory drive may change dramatically without sedation. Rather, a tube compensation option that adjusts additional pressure based on the patient's flow demand minimally disrupts the patient's natural sinusoidal flow pattern.

Although a recent RCT did not find meaningful differences in outcome between no sedation and light sedation with daily interruption, this study excluded patients who required sedation for improved oxygenation.[17] Additionally, primary brain-injured patients had little representation in the sample. Brain-injured patients may be more susceptible to delirium and early rehabilitation may have a more important effect on outcome.[18] In a prospective study of 240 patients, APRV was associated with significant lower median doses of analgesia and sedation when compared with conventional LTV.[15] In the RCT by Zhou et al, patients in the APRV arm used significantly less midazolam and fentanyl compared with the LTV group.[2]

Acid–Base Consequences of LTV

An accepted consequence of reduced minute ventilation with LTV is hypercapnic acidosis. The effects of hypercapnic acidosis in patients with acute cerebral injury have not well elucidated. Hypercapnic acidosis may cause toxic intracellular calcium influx, excitotoxic glutamate release, and apoptosis[19]. In a large retrospective study of 30,742 patients with cerebral injury, hypercapnic acidosis within the first 24 hours of intensive care unit stay was associated with an increased odds ratio of mortality when compared with normocapnia and normal pH. Adjusted mortality increased with increasing partial pressure of carbon dioxide in patients with hypercapnic acidosis.[19]

In APRV, arterial carbon dioxide often normalizes or is reduced (►**Table 1**). A prolonged inspiratory time leads to alveolar recruitment and collateral ventilation; and this effect is especially notable in lung units with reduced compliance.[4,20] These favorable changes reduce dead space ventilation and increase alveolar surface available for gas exchange.[2,4]

APRV Limits Oxygen Toxicity

Initial ventilation with APRV may alleviate the need for chronically high FiO_2 during times of lung injury. In patients with highly noncompliant lungs, the maximum plateau pressure goal or ICP may limit the amount of extrinsic PEEP available for use. Given that patients with acute cerebral injury have a lower threshold to tolerate hypoxemia[21,22] compared with other patients, in which lower oxygen saturations may be tolerated, FiO_2 may be kept at relatively high levels for longer periods of time. Conversely, hyperoxia is also deleterious to the injured brain.[23,24] In a retrospective study of severe traumatic brain injury patients monitored with cerebral microdialysis (CMD), incremental FiO_2 was associated with cerebral excitotoxicity as measured by CMD glutamate. Even in patients with brain hypoxia, as measured by brain tissue oxygen tension, FiO_2-related increases of CMD glutamate were significant starting at an FiO_2 of 60%.[24] This data are consistent with a retrospective study of postcardiac arrest patients that found those with higher exposure to inspired oxygen had worse neurological outcomes.[25] APRV may alleviate this issue by more efficient oxygen delivery and less need for higher FiO_2.[26]

Limitations and Conclusion

APRV may offer several benefits over LTV in patients with cerebral injury (►**Table 2**). However, there are several limitations with APRV that are worth noting. First, there may be limited benefit of using APRV over conventional modes in the absence of sufficient spontaneous breathing. For example, in patients with limited spontaneous breaths, there may be an increased risk of hypercapnia if the P_{high} is set too low or T_{high} is set too long. This may occur, for example, in a patient who requires excess sedation for status epilepticus or who has an ICP crises requiring deeper levels of sedation. Second, the T_{low} may vary despite the ventilator setting due to an intrinsic synchronization feature in some ventilators. This may lead to an unreliable generation of total PEEP.[27] This may specifically be a concern in patients who require a prolonged expiratory time such as those with obstructive lung disease (e.g., chronic obstructive pulmonary disease). Third, the effects of spontaneous breathing over the P_{high} on transpulmonary pressure swings need further study.[27,28] Finally, spontaneous breathing may lead to volutrauma and increased work of breathing. For example, if a patient with brain injury has associated cardiac dysfunction such as neurogenic stunned myocardium following aneurysmal subarachnoid hemorrhage, excess spontaneous breathing may be deleterious for cardiac work. Therefore, APRV is best suited for patients who would benefit from the aforementioned physiological benefits but is contraindicated in patients who need deep sedation, have obstructive lung pathology, or who may be harmed from excess spontaneous breathing.

Table 2 Potential benefits of APRV over LTV ventilation in brain-injured patients

Pitfall of LTV	Alternative strategy using APRV
High sedation requirements due to high intrinsic respiratory drive limiting accurate neuromonitoring	Lessened sedation requirements compared with LTV
Clearance of secretions during inspiratory phase of respiratory cycle may lead to ventilator dyssynchrony	Clearance of secretions feasible throughout the respiratory cycle due to an open loop system
Low tidal volumes may lead to hypercapnic acidosis which may be particularly harmful to brain-injured patients	Avoidance of hypercapnic acidosis due to longer diffusion times and spontaneous breathing
Higher FiO_2 requirements compared with APRV, especially in PEEP limited patients such as those with ICP crises	Lower FiO_2 requirements compared with LTV due to higher mean airway pressures

Abbreviations: APRV, airway pressure release ventilation; FiO_2, fractional inspired oxygen; LTV, low tidal volume; PEEP, positive end-expiratory pressure.

The overall level of evidence supporting the use of APRV in brain-injured patients is low and is derived primarily from small studies (►**Table 1**). Further, APRV was applied in these patients due to hypoxemia in the setting of compromised lung compliance and the effects of APRV outside of these patients, such as those with elevated ICP and normal lung compliance, are unknown. Lack of high-level evidence, however, remains equally problematic for LTV and other conventional modes of mechanical ventilation in brain-injured patients, as these patients are excluded from RCTs[1,2] Unlike in populations studied in lung protective mechanical ventilation trials, there is no evidence favoring one mode of mechanical ventilation over another in terms of functional neurological outcome or mortality. Therefore, one should not conclude one mode is superior to another in brain-injured patients based on the available evidence. Rather, this review highlights some potential physiological benefits of APRV over LTV in this patient population (►**Table 2**) extracted from the available evidence.

A large, prospective observational cohort would further clarify the role of APRV in patients with cerebral injury and an RCT comparing APRV to LTV including brain-injured patients is necessary to move beyond equipoise. In the interim, intensivists should keep APRV in their armamentarium for brain-injured patients. Readers should refer to a landmark review article for further details regarding initial settings and troubleshooting APRV.[4] Ultimately, careful consideration should be made to tailor the mode of mechanical ventilation to the individual need of the patient.

Conflict of Interest
None declared.

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