Airway pressure release ventilation and biphasic positive airway pressure ventilation are being used increasingly as alternative strategies to conventional assist control ventilation for patients with acute respiratory distress syndrome (ARDS) and acute lung injury. By permitting spontaneous breathing throughout the ventilatory cycle, these modes offer several advantages over conventional strategies to improve the pathophysiology in these patients, including gas exchange, cardiovascular function, and reducing or eliminating the need for heavy sedation and paralysis. Whether these surrogate outcomes will translate into better patient outcomes remains to be determined. The purpose of this review is to summarize the rationale behind the use of these ventilatory strategies in ARDS, the clinical experience with the use of these modes, and their future applications in trauma patients.

Key Words: Acute respiratory distress syndrome, airway pressure release ventilation, mechanical ventilation.

Airway pressure release ventilation (APRV) is a mode of mechanical ventilation designed to allow patients to breathe spontaneously while receiving high levels of continuous positive airway pressure (CPAP). This ventilator mode was first proposed by Downs and Stock in 1987 after study in canines with acute lung injury as a means to augment alveolar ventilation while allowing spontaneous respiratory efforts throughout an inverted mechanical ventilatory cycle. Biphasic positive airway pressure ventilation (BIPAP) is similar to APRV in allowing spontaneous breathing, but there are no restrictions on the timing of the pressure release. Thus, in BIPAP, spontaneous breathing efforts may be present during the longer release phase. These ventilator modes have been increasingly studied in critically ill patients with acute lung injury, gaining popularity because of their ability to reduce sedation and neuromuscular blockade. Most recently, a retrospective review demonstrated that APRV was a safe alternative for traumatically injured patients at high risk for acute lung injury/acute respiratory distress syndrome. The goal of this review is to provide a summary of the pathophysiologic basis for the use of these ventilatory modes in ARDS, discuss the implicit advantages of spontaneous breathing with these ventilator strategies, and review the recent clinical experience with APRV and BIPAP in critically ill patients.

Acute Lung Injury and Acute Respiratory Distress Syndrome

Acute lung injury is characterized by a heterogeneous pattern of diffuse alveolar damage resulting from either a direct, indirect, or a combination of insults to the lung. Well described by Gattinoni and colleagues, the injured lung in acute respiratory distress syndrome (ARDS) is heterogeneous in gas and fluid distribution, with variable computed tomography findings within individual patients, depending upon the cause of ARDS. With direct insults (e.g., pneumonia), multifocal parenchymal involvement is found, whereas indirect insults (e.g., sepsis) result in a more diffuse, interstitial pattern of injury. Compared with healthy volunteers, total lung volume, including both aerated and nonaerated portions, is reduced by more than 20% in patients with acute lung injury.

Because no effective pharmacologic therapy has been identified, treatment is primarily supportive. To ameliorate the derangements in gas exchange, lung compliance, and work of breathing, intubation, and mechanical ventilation are often required. Arterial desaturation, the hallmark of ARDS, can usually be improved to safe levels by increasing the fraction of inspired oxygen (FiO₂) and by applying positive end-expiratory pressure. The characteristic increase in ventilatory requirements, which is caused by an increase in physiologic dead space, can be supported using a variety of ventilator modes, including both volume-cycled and pressure-limited ventilation. Unfortunately, regardless of which ventilatory mode is used, mechanical ventilation may also cause lung injury.
The elevated airway pressures and supraphysiologic end-inspiratory volumes encountered during positive pressure ventilation have been implicated as secondary sources of direct lung injury, termed barotrauma and volutrauma, respectively. In the past, a variety of forms of ventilator-associated barotrauma (including pneumothoraces, pneumomediastinum, interstitial air, or subcutaneous emphysema) have been associated with and ascribed to peak airway pressures >50 cm H2O.10–12 More recently, excess end-tidal alveolar stretch appears to be one of the most important factors causing lung injury, evidenced by the reduction in ARDS mortality found with low tidal-volume (and low end-inspiratory alveolar pressure) ventilation strategies.13–15

Dreyfuss and colleagues elegantly demonstrated that excessive tidal volume during mechanical ventilation was responsible for lung injury independent of the absolute alveolar pressure.16 To test this hypothesis, ventilation with high pressures and high volumes was compared with ventilation with high pressures and low lung volumes. Lung volume was kept constant in one group of rats by strapping the chest and abdomen circumferentially, dissociating the change in alveolar pressure from lung volume. Although the high volume group suffered lung injury, the low volume group did not. Lung injury was quantified using microvascular permeability and water accumulation in the lung, and was only seen in alveoli that were overdistended regardless of the alveolar pressure.16

Overdistension lung injury is associated with a variety of pathophysiologic abnormalities including an increase in endothelial permeability,17,18 rupture of the alveolar-capillary barrier,19 and exacerbation of the local inflammatory cascade.20,21 Given the heterogeneous nature of the pulmonary infiltrates found in radiographic studies of ARDS patients and the regional differences in compliance that are associated,22 it is thought that certain lung regions may be more susceptible to the ventilator-associated alveolar overdistension, particularly those regions most anterior in the thorax and those bordering regions of alveolar collapse.23

In addition to volutrauma caused by regional overdistension, the repetitive opening and closing of atelectatic lung units, called atelectrauma, has also been implicated as an important mechanism for ventilator-induced lung injury (VILI).24 This injury pattern has been ascribed to the excessive shear force applied to lung tissue immediately adjacent to atelectatic regions during tidal ventilation.24 Theoretical predictions of the magnitude of the shear force applied to the parenchymal tissue in these juxtaposed regions suggest pressures in excess of 100 mm Hg.25 Although there is ample experimental data to support the clinical significance of this form of VILI, at present there is no definitive evidence that altering ventilatory strategy to reduce atelectasis (e.g., with use of high levels of positive end-expiratory pressure [PEEP] or recruitment maneuvers) can reproducibly improve clinical outcomes. Similarly, although there is clear physiologic rationale and convincing experimental data from animal models to support the use of the prone position to ameliorate VILI by reducing the heterogeneity in ventilation and lung mechanics,25 clinical trials have not yet demonstrated that this intervention improves patient outcomes.26

At present, the evidence from large randomized clinical trials supports the use of assist control volume-cycled ventilation alone as the default mode for patients with ARDS.27 With this modality clinicians must employ a specific ventilatory prescription to adequately support arterial oxygenation, while limiting tidal elevations in alveolar pressure (≤30 cm H2O) with the use of low tidal volumes (~6 mL/kg/predicted body weight). In those patients whose alveolar pressures do not exceed 30 cm H2O, it is not clear whether it remains important to maintain the tidal volume at 6 mL/kg/PBW goal.28 In addition, some minimal amount of PEEP should be used to reduce atelectrauma; however, the magnitude of pressure required to minimize injury or the methodology on how to titrate this pressure is not known.9 Other modes of ventilation have not conclusively shown benefit on patient outcome in large scale trials, yet alternative modes such as APRV and BIPAP, which have compelling evidence from animal models, may offer a better solution for ventilatory support in patients with ARDS.

APRV and BIPAP

APRV and BIPAP are offered on several commercially available ventilators that have active exhalation valves, including the Puritan Bennett 840,29 the Servo i (Maquet Critical Care, Bridgewater, NJ),30 the Dräger Evita XL (Drager Medical, Inc. Telford, PA),31 the VIASYS Avea + (VIASYS Healthcare, Conshohocken, PA),32 and the Hamilton Galileo (Hamilton Medical, Rhamsums, Switzerland).33 These are all characterized as pressure-limited, time-cycled, spontaneous modes of ventilation. The unique features of these ventilator modes that are most significant for patients with acute lung injury include (1) spontaneous breathing, and (2) tidal ventilation to accomplish CO2 clearance occurs in reverse sequence from other conventional modes, starting from a higher “baseline” pressure and occurs as a decompression-reinflation tidal cycle or expiration-inspiration (Fig. 1).34 Biphasic positive airway pressure ventilation is also termed Bi-Vent (Servo i), BIPAP (Drager Evita XL), BiLevel (Puritan Bennett), BiPhasic (Viasys Avea), and DuoPAP (Hamilton). This is not to be confused with bilevel positive airway pressure (BiPAP), a noninvasive ventilation system offered by Respirronics (Carlsbad, CA).35 BIPAP will be the preferred abbreviation for this review. Although not currently available, the Servo 300A ventilators offer synchronized intermittent mandatory ventilation (SIMV) – pressure control + pressure support (PS), which is similar to APRV and BIPAP by allowing spontaneous, pressure-supported breaths between mechanical, pressure-regulated breaths.36

When implementing these alternative modes of ventilation, the clinician’s ventilatory prescription is very different from conventional settings. The clinician sets a high CPAP level (P_high) to accomplish oxygenation goals,24 and sets both
the timing and duration of the pressure release (P\text{low}) for ventilation goals. These parameters form a ventilator phase cycle, composed of the inspiratory phase (during P\text{high}) and a release phase (during P\text{low}). A short release time and predominance of T\text{high} is the fundamental strategy used to improve oxygenation. As release time and frequency decrease, mean airway pressure increases, which results in lung recruitment. This strategy may be limited by the reduction in minute ventilation induced by these ventilator settings. However, by using an active exhalation valve, these systems allow the patient to breathe spontaneously throughout the phase cycle (Fig. 1). As such, patients maintain control of the timing of their spontaneous breaths independent of the physician-determined lengths of both P\text{high} and P\text{low}. In addition, the transition from P\text{high} to P\text{low} is synchronized with patient breathing by the ventilator when possible, through the detection of airway pressure changes and set times for P\text{high} and P\text{low}. Total delivered mechanical tidal volume is dependent on thoracic compliance, airway resistance, and the duration and timing of the pressure release maneuver. As with traditional pressure-regulated ventilator modes, elevated airway pressures (peak and plateau) and excessive tidal volumes should be avoided; however, the independent effect of tidal volume, when plateau pressure is controlled, remains controversial. Biphasic positive airway pressure ventilation only differs from APRV in that the duration of P\text{low} is longer (Fig. 1). This fundamental difference results in lower mean airway pressure and augmented negative intrathoracic pressure from spontaneous breaths on P\text{low} during BIPAP. In both APRV and BIPAP, spontaneous breaths can be pressure supported. The pressure support directly augments the spontaneous breaths from P\text{low} as with conventional CPAP, whereas the pressure assist from P\text{high} is restricted to P\text{supp} (P\text{high}− P\text{low}), so that the airway pressures achieved during spontaneous breaths taken from P\text{high} do not exceed those achieved during breaths taken from P\text{low}. However, on some ventilators, the pressure support available on P\text{high} is limited further to a fixed pressure value of 1.5 cm H\text{2O}.

Both ventilator strategies can be illustrated using the pressure-volume (P/V) curve as a theoretical guide to airway pressure boundaries during both mechanical inspiration and intermittent pressure release. In principle, practitioners would set P\text{high} on the upper end of the linear portion of the P/V curve, just below the upper inflection point. P\text{low} would be set at the lower end of the same linear segment, presumably just above the lower inflection point to prevent cyclic recruitment/derecruitment injury. Although the P/V curve is a useful conceptual guide to adjusting ventilator settings, utilizing the P/V curve to determine inflection points at the bedside is limited by technical considerations, reliability of finding the lower inflection point, and uncertainty regarding the true meaning of these transition points, such as whether the upper inflection point represents the end of alveolar recruitment or the start of lung overdistension. In addition, many have argued that PEEP should be set by the inflection point on the expiratory limb of the P/V curve. Despite these issues, the P/V curve has been used to guide the initial airway pressure settings in clinical trials of APRV and BIPAP. Protocols for the initiation of APRV and BIPAP have been employed in human trials; however, their variability prohibits a single recommended method. In Figure 2, the ventilator display (Puritan Bennett 840) of a patient recently transitioned to APRV is shown to demonstrate the initial ventilator settings used.

Weaning from APRV or BIPAP can be accomplished using a “drop-and-stretch” method. Patients who meet traditional ventilatory weaning goals for oxygenation (F\text{O2} ≤ 50%) and are adequately awake may tolerate reductions in P\text{high} while extending T\text{high}, allowing a gradual increase in spontaneous minute ventilation. In patients who require higher P\text{low}, simultaneous reductions will help reduce mean airway pressure. Monitoring of oxygenation during P\text{low} reductions is required if patients are at risk for derecruitment, whereas PaCO\text{2} may increase if patients do not respond with an increased spontaneous ventilation to compensate for the reduction in minute ventilation resulting from an extension of T\text{high}. When mechanically delivered breaths account for a minimal proportion of total minute ventilation, patients may be transitioned to CPAP (with automatic tube compensation) or pressure support ventilation (PSV).

Fig. 1. Airway pressure tracing of both airway pressure (P\text{aw}) release ventilation and biphasic positive airway pressure ventilation. Wave form fluctuations in P\text{aw} signify spontaneous breathing.
Benefits of Spontaneous Breathing During Mechanical Ventilation

Spontaneous breathing during mechanical ventilation has many advantages. Diaphragmatic contraction serves as a more efficient means of acquiring tidal volume than through positive pressure ventilation (PPV), by increasing the recruitment of atelectatic lung in dependent regions. Using ultrasound measurements, Jousela and colleagues performed a series of studies which demonstrated a direct relationship between inspired volume and diaphragmatic excursion, as well as the need for greater mechanical volumes to achieve equal excursion as to spontaneous effort.47 Phrenic nerve stimulation during halothane anesthesia can decrease the volume of atelectatic lung by 30% in patients without disease.48 Kleinman and colleagues used diaphragmatic fluoroscopy to compare excursion between chronic obstructive pulmonary disease (COPD) patients and healthy subjects when breathing spontaneously or after paralysis and mechanical ventilation. Although no difference in regional excursion was present between COPD and non-COPD patients, total diaphragmatic displacement was increased in spontaneous breaths compared with PPV, and the pattern of displacement favored dependent regions of the lung.49 Because nonaerated lung increases along a sternovertebral gradient in acute lung injury,50 augmentation of diaphragm movement through spontaneous effort may appropriately target atelectatic lung in ARDS.

Effects of Spontaneous Breathing During APRV and BIPAP

When spontaneous breathing is superimposed upon pressure-controlled ventilation as in APRV or BIPAP, the benefits manifest across many organ systems. In the lung, improved matching of ventilation and perfusion has been demonstrated in both animal models and human studies. Downs and Stock compared APRV, SIMV, and PSV at a similar minute ventilation in canines with acute lung injury. They found that PaCO₂ was lower on APRV, consistent with a reduction in physiologic dead space when compared with the other modes of ventilation.1 This finding in dogs was confirmed in humans by demonstrating a 6% to 7% reduction in dead space in postoperative cardiac surgery patients ventilated with APRV compared with PSV or SIMV.51 Using an oleic acid lung injury model, canines had improved ventilation-perfusion (V/Q) matching when breathing spontaneously on BIPAP ventilation compared with assisted breathing on PSV at equal airway pressure limits.52 Putensen and colleagues performed inert gas analysis in human patients on APRV with spontaneous breathing, APRV without spontaneous breathing, and PSV at equal airway pressures and minute ventilations. Most notably, intrapulmonary shunt was decreased by 7% in APRV with spontaneous breathing, and dispersion of the ventilation and perfusion distributions was significantly reduced compared with APRV without spontaneous breathing.53 This was attributed to both an increase in ventilation of well-perfused lung units and recruitment of nonventilated units with spontaneous breathing. Because diaphragmatic work may be maximal during breath triggering while on P_{high}, the application of pressure support to assist spontaneous breathing may negate the improvements in ventilation perfusion matching seen by Putensen et al.53 Wrigge and colleagues used computed tomography densitometry to demonstrate higher end-expiratory lung volume in animals who spontaneously breathed on APRV than those who did not (752 ± 203 vs. 353 ± 104 mL, p < 0.01). Figure 3 shows that the volume of nonaerated lung was significantly greater without spontaneous breathing, and that the mean overall lung density (1/aeration) was lower with spontaneous breathing on APRV.54 This may have been demonstrated in patients by the findings of Dart et al., where the PaO₂/FiO₂ ratio significantly increased (23%) after 72 hours of implementation of APRV in high-risk trauma patients.2 In addition to improvements in gas exchange, APRV and BIPAP can lower airway pressures. The earliest human trial of APRV by Garner and colleagues found that peak airway pressures were reduced when compared with conventional
Effects of APRV and BIPAP on the Cardiovascular System

The decrease in intrathoracic pressure associated with spontaneous breathing also has significant effects on the cardiovascular function of patients on APRV or BIPAP. Initial studies of APRV, which focused on safety, evaluated the impact on hemodynamics of transitioning from PPV to APRV. No adverse hemodynamic consequences were found in early animal and human trials of APRV compared with either spontaneous breathing or PPV. In fact, 24 patients with ARDS on APRV with spontaneous breathing had an increase in their cardiac index (5.6 vs. 5.0 L/min/m², \( p < 0.05 \)), right ventricular ejection fraction (41 versus 32%, \( p < 0.05 \)), and right ventricular end-diastolic volume index (136 versus 123 mL/m², \( p < 0.05 \)) compared with APRV without spontaneous breathing. These changes in venous return and cardiac output, coupled with an increase in recruitment of atelectatic lung, likely contribute to the improvement in arterial oxygenation in APRV with spontaneous breathing. Noting that oxygen consumption (\( VO_2 \)) is not increased during spontaneous breathing with APRV, the aforementioned increase in oxygen delivery results in a decreased oxygen extraction ratio (23 ± 1% vs. 21 ± 1%, \( p < 0.05 \)) compared with PSV. A reduction in venous admixture (\( Q_s/Q_t \)) and \( AaDO_2/FiO_2 \) was also evident after initiation of APRV, improving from onset to 8 hours (\( AaDO_2/FiO_2 \): 487 vs. 414 mm Hg, \( p < 0.01 \); \( Q_s/Q_t \): 20.6 vs. 13.9%, \( p < 0.02 \)). This was attributed to an increase in shunt fraction (12% vs. 7%) and V/Q mismatch on APRV, which the authors hypothesized was because of an increase in atelectasis associated with the rapid pressure release maneuver. As such, they recommended minimization of mechanical breaths during the APRV mode.

Effects of APRV and BIPAP on Renal Function and Gastrointestinal Perfusion

The advantages of spontaneous breathing on APRV are not limited to the thorax. Effective renal blood flow, as measured by para-amino hippurate, was significantly increased (858 ± 388 vs. 714 ± 236 mL/min/m², \( p < 0.01 \)) and glomerular filtration rate, measured by inulin clearance, was higher (94 ± 47 vs. 82 ± 35 mL/min/m²) with the addition of spontaneous breathing during APRV compared with APRV without spontaneous breathing in acute lung injury (ALI) patients with no pre-existing renal dysfunction. This benefit was attributed to improvement in systemic blood flow and arterial blood oxygenation. Patients were ventilated with \( P_{low} \) of approximately 16 mm Hg, but the study design did not investigate how renal perfusion was altered by incremental increases in \( T_{high} \), \( P_{high} \), or \( P_{low} \). These findings extend the conclusions of Steinhoff and colleagues, who demonstrated improvement in renal function after transitioning from full support to intermittent mandatory ventilation with spontaneous breathing. Intestinal perfusion is also enhanced with APRV and spontaneous breathing. Using the oleic acid, porcine lung injury model, Hering and colleagues confirmed increases in mean arterial pressure, intrathoracic blood volume, and cardiac output, whereas reporting increased mucosal-submucosal blood flow to stomach, small, and large bowel.

Impact of APRV and BIPAP on Requirements for Sedation and Neuromuscular Blockade

Recognizing the importance of limiting sedation and neuromuscular blockade in critically ill patients receiving mechanical ventilation, APV and BIPAP are unique in allowing a prolonged inspiratory phase without requirements for heavy sedation and paralysis. Recent studies tested the hypothesis that the decreased requirements for these agents while ventilating with APRV and BIPAP may improve long-
term outcomes and facilitate weaning. Putensen and colleagues randomized 30 trauma patients at risk for ARDS to either APRV or pressure control ventilation (PCV) and studied sedation requirements and ventilator outcomes. They report a reduction in mean ventilator duration by 6 days, a reduction in mean intensive care unit (ICU) duration by 7 days, and lower total infusion requirements for sufentanil and midazolam in patients ventilated with APRV and spontaneous breathing. Of note, a higher proportion of patients ventilated with PCV developed ARDS, perhaps reflecting a sicker cohort; however, the authors conjecture that these patients may have fulfilled criteria for ARDS as a result of the associated gas exchange and cardiopulmonary dysfunction encountered with PCV compared with APRV. In another pilot study by Kaplan et al., ARDS patients who were already paralyzed and sedated with inverse-ratio ventilation were transitioned to APRV, with an approximate 50% reduction in vasopressor use (epinephrine, norepinephrine), 70% reduction in neuromuscular blockade, and 30% reduction in sedation (benzodiazepines) needed to maintain a constant stimulated bispectral index (BIS) value of 70. These findings are supported by a prospective cohort study in postoperative cardiac surgery patients, which demonstrated a reduction in ventilator days and total benzodiazepine use in patients managed with BIPAP. Despite the small sample size, use of historical controls, and lack of randomization in these investigations, the results suggest that sedation/neuromuscular blockade requirements are dramatically reduced with APRV/BIPAP and that this may be associated with improved patient outcomes. These results are compelling; however, the above-mentioned limitations suggest the interpretation of their results require caution.

Potential Limitations of APRV and BIPAP

Because APRV and BIPAP are pressure-controlled ventilator modes, tidal volume is variable. As such, there is a potential risk of delivering excessive tidal volumes to patients when using these modes. Because mechanically delivered tidal volumes are dependent on lung compliance, preset levels of $P_{\text{high}}$ and $P_{\text{low}}$, and the release time, if lung or chest wall compliance improves, tidal volume will increase in proportion. The importance of excess tidal volumes ($>6 \text{ mL/kg/PBW}$) in patients who have low ($<30 \text{ cm H}_2\text{O}$) airway pressure is controversial, but remains an issue with pressure-controlled modes; an exception is the dual modes of ventilation, which allow volume to be preset, including pressure-regulated volume control and volume-control plus. Use of these dual modes, in contrast, may result in excessive end-inspiratory pressures. On APRV or BIPAP, a reduction in respiratory system compliance that would reduce mechanically-delivered tidal volume ($V_T$) would likely be compensated for by an increase in spontaneous ventilation. With pressure-supported spontaneous breaths, potentially dangerously high tidal volumes may be generated at the $P_{\text{high}}$ setting. For instance, as shown in Figure 4, Neumann et al. reported airway pressure, flow, and volume tracings that clearly demonstrate aggregate tidal volumes approaching 1 L during spontaneous breathing on $P_{\text{high}}$. The authors do not report whether these tracings are from a patient with ALI or COPD, nor the ideal body weight of this subject. It is not known whether this represents a real problem in clinical practice, and available reports of spontaneous tidal volumes in human studies of APRV and BIPAP have not distinguished between breaths on $P_{\text{high}}$ versus $P_{\text{low}}$. Theoretically, in patients with ALI, vigorous respiratory efforts from $P_{\text{high}}$, with or without pressure-support on $P_{\text{high}}$, could result in excessive transpulmonary pressures to cause regional overdistension and contribute to lung injury. However, this may also occur during volume-cycled ventilation when patients exert vigorous efforts during inhalation.

In addition, shearing of terminal lung units and vascular endothelium may occur during rapid deflation below some lower inflection point (LIP) of the pressure-volume curve. This has the potential to occur during the release phase of APRV. In particular, patients in whom $P_{\text{low}}$ is set below the theoretical LIP or in whom $P_{\text{low}}$ is arbitrarily placed at zero-end expiratory pressure may be at higher risk, providing there is sufficient time to reach FRC. Notably, no consensus exists as to the proper setting of $P_{\text{low}}$, and many human trials have used very low pressure settings for the initial $P_{\text{low}}$. 

![Fig. 4. Mechanical breaths shown on $P_{\text{aw}}$ tracing. Breath (B on flow tracing) is spontaneous effort on $P_{\text{high}}$. Net tidal volume of mechanical and spontaneous breaths are approximately 900 mL. (Adapted from Neumann et al. with permission from Springer Science and Business Media.)](image-url)
Table 1: Investigational Studies of APRV or BIPAP in Human Adult Patients

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<td>PIP and PEEP reduced and mean P_{aw} increased at 2 hours; no difference in gas exchange or hemodynamic variables</td>
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<td>Sydow et al.57</td>
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<td>Moderate to severe acute lung injury; FiO2 = 1.0, AaDO2 &gt;300</td>
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<td>Calzia et al.73</td>
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<td>ARDS with leukopenic (WBC &lt;1,000 cells/µL), MV &lt;24 hours</td>
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<td>Rathgeber et al.71</td>
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<td>Prospective cohort trial, SIMV vs. CMV vs. BIPAP</td>
<td>596</td>
<td>Postoperative cardiac surgery patients, n = 42 on BIPAP</td>
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<td>Hormann et al.77</td>
<td>1997</td>
<td>Prospective, crossover trial; BIPAP to PC-IRV to BIPAP</td>
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<td>No difference between VO2, EE, VCO2, or Q/R between modes</td>
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<td>Prospective, randomized trial; PSV vs. APRV with and without spontaneous breathing using identical P_{aw} limits and V_E</td>
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<td>Multiple trauma (66%) with ARDS, sedated to Ramsay = 4</td>
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<td>Acute lung injury, Ramsay = 3</td>
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Table 1: Investigational Studies of APRV or BIPAP in Human Adult Patients (continued)

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<td>Putensen et al.45</td>
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<td>Neumann et al.37</td>
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<td>Prospective trial; APRV with varying release times (Tlow) on gas exchange and breathing pattern</td>
<td>28</td>
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<td>Reduction in Tlow, associated with increase in contribution of spont. Ve to total VE; patient I:E ratio unaffected by Tlow</td>
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<td>Acute lung injury, Ramsay = 4</td>
<td>Effective renal blood flow, GFR increased with spontaneous breathing</td>
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<td>Varpula et al.36</td>
<td>2003</td>
<td>Prospective, randomized trial; SIMV-PC/PS vs. APRV; patients in both arms subject to prone position if P/F ratio &lt;200 mm Hg</td>
<td>24</td>
<td>Medical/surgical patients, acute lung injury = PaO2/FiO2 &lt;300, PCWP &lt;18, bilateral infiltrates</td>
<td>33 of 45 underwent proning; prone positioning feasible in APRV; prone after 24 hours of APRV &gt; improvement in PaO2/FiO2 ratio</td>
</tr>
<tr>
<td>Varpula et al.75</td>
<td>2004</td>
<td>Prospective randomized trial; APRV vs. SIMV as primary ventilatory mode</td>
<td>58</td>
<td>Acute lung injury patients</td>
<td>No difference in primary outcome = ventilator free days at day 28</td>
</tr>
<tr>
<td>Dart et al.2</td>
<td>2005</td>
<td>Retrospective cohort; transition to APRV for 72 hours from conventional mode</td>
<td>46</td>
<td>High risk multitrauma patients; mean PaO2/FiO2 = 243</td>
<td>Improved PaO2/FiO2 ratio at 72 hours, safe alternative</td>
</tr>
</tbody>
</table>

AaDO2, alveolar arterial oxygen gradient; ALI, acute lung injury; APRV, airway pressure release ventilation; ARDS, acute respiratory distress syndrome; ATC, automatic tube compensation; BIPAP, biphasic positive airway pressure; CI, cardiac index; CPAP, continuous positive airway pressure; CMV, controlled mandatory ventilation; COPD, chronic obstructive pulmonary disease; DO2, oxygen delivery; EE, energy expenditure; FiO2, fraction of inspired oxygen; GFR, glomerular filtration rate; ICU, intensive care unit; IMV, intermittent mandatory ventilation; MV, mechanical ventilation; NM, neuromuscular; PaO2, partial pressure arterial oxygen; PaCO2, partial pressure arterial carbon dioxide; Paw, airway pressure; PC, pressure-controlled; PC-IRV, pressure-controlled inverse ratio ventilation; PEEP, positive end-expiratory pressure; PPV, positive pressure ventilation; PS, pressure support; RQ, respiratory quotient; SIMV, synchronized intermittent mandatory ventilation; VC-IRV, volume cycled inverse ratio ventilation; Vd/Vt, dead space to tidal volume ratio; Ve, minute ventilation; VO2, oxygen consumption; VCO2, carbon dioxide production; VT, tidal volume; V/Q, ventilation perfusion; WBC, white blood cell count.

Habashi argues, however, that the resistive load of the artificial airway sufficiently delays expiration to prevent derecruitment even if Plow is set at 0 cm H2O.46

Calzia et al. have also reported that the energy cost of breathing for patients on BIPAP is higher than for those breathing with PSV.73 Measured under comparable conditions (airway pressure [Psw] and minute ventilation [VE]), the pressure time product was elevated during BIPAP compared with PSV, perhaps suggesting that the mechanical support of spontaneous breaths during PSV incurred less respiratory work. Of note, this increased work of breathing did not translate into higher VO2 or VCO2 in the investigation by Staudinger et al., bringing into question the clinical relevance of this finding.74 More importantly, in both of these studies, the spontaneous breaths were not augmented by pressure support, which likely explains the findings. Because some pressure support augments most spontaneous breaths in clinical practice when using these ventilator modes, the significance of these findings is minimized. It is important to note that if pressure support is applied to spontaneous breaths during Phigh, patient effort will be uncoupled from airway pressure and flow development, which may negate the benefit to ventilation and perfusion matching reported by Putensen et al.52

Patients with obstructive lung disease may require closer monitoring while receiving APRV and BIPAP. Physician determination of the release time (Tlow) ideally provides adequate time for CO2 clearance, yet not too long to allow derecruitment. However, the increased expiratory resistance and flow limitation makes it challenging to achieve both of these goals. Neumann et al. demonstrated elevation in PaCO2 with release times <1.0 second in a subset of COPD patients. This response would be most likely to occur when respiratory drive is blunted by sedation.37 Although awake patients may compensate for this problem by increasing spontaneous ventilation, this may lead to excessive work of breathing as suggested by Calzia et al.73 Further study is needed to deter-
mine whether the changes in arterial blood gases have clinical significance in this patient subset.

Adverse events associated with the use of APRV or BIPAP have been reported rarely in human studies. In 1991, Rasanen et al. documented inadequate ventilation in 3 of 50 patients transitioned to APRV, requiring return to conventional positive airway pressure ventilation.59 This problem was also experienced by Cane et al. in 1 of 18 patients; in the same study, 2 of 18 patients developed inspissated secretions with basilar lobar atelectasis.50 After return to conventional positive pressure ventilation with bronchial hygiene therapy, collapsed lobes were re-expanded without further complication. Additionally, the retrospective review by Dart et al. reported that APRV had to be terminated in a patient with closed head injury because of an associated increase in intracranial pressure; it is not clear whether the rise in intracranial pressure was because of an increase in pCO2 or a decrease in venous return because of an elevated intrathoracic pressure.2 No other complications have been reported in recent investigations of long-term ventilation for up to 10 days with APRV and BIPAP.45,70

Recommendations for Future Investigations

To our knowledge, 20 human trials of APRV and BIPAP are published in the literature (Table 1).2,3,6,36,37,45,51,53,55–59,61,65,70–71,73–77 none of which have included more than 60 patients on these ventilator modes. Given the associated outcome benefits of using less sedative and paralytic medications, the use of APRV or BIPAP in patients with ARDS or ALI is very attractive. In addition, if cardiac output and regional organ perfusion can be preserved or augmented using these modes with spontaneous breathing, then there exists a potential for reduced organ dysfunction and mortality in larger clinical trials. It seems as though the initiation of APRV and BIPAP are often “last ditch” efforts in the patient with refractory hypoxemia who has failed using conventional modes. The randomization of patients early on in ARDS is essential to study these important clinical endpoints such as organ dysfunction, sedative use, ICU length of stay, mortality, and cost savings when compared with conventional ventilatory strategies. One such trial by Varpula et al. was recently published that demonstrated no difference in clinical outcomes (ventilator-free at day 28, all physiologic variables) when patients were randomized to APRV versus SIMV after meeting ALI criteria.75

CONCLUSIONS

APRV and BIPAP ventilation are unique approaches to ventilatory support in patients with acute lung injury, allowing patients to spontaneously breathe during the entire phase cycle. Proposed benefits of spontaneous breathing are wide-ranging, and have been documented in multiple animal studies and small human trials. Most exciting, APRV and BIPAP offer a potential way to limit neuromuscular blockade and sedation use, perhaps facilitating weaning from mechanical ventilation and improving long-term outcomes in patients with severe lung injury. In addition, the improvements in cardiac output and organ blood flow resulting from spontaneous breathing efforts suggest that these modes may possibly ameliorate the organ dysfunction common in patients with ARDS. As larger randomized trials are proposed to evaluate APRV and BIPAP in ARDS, we recommend close monitoring of mechanical and spontaneous tidal volumes to ensure that this ventilatory strategy remains lung protective.

REFERENCES


EDITORIAL COMMENT

In the European Union, APRV is known as bilevel positive airway pressure (BIPAP) and is not to be confused with the noninvasive ventilation (BiPAP) used in the United States. Although seemingly complex, APRV is a mode with which we are familiar: continuous positive airway pressure (CPAP). APRV is CPAP that occurs at a greater pressure but is periodically turned off to allow CO₂ clearance (ventilation).¹ Villar et al. reviewed the powerful ability of constant gas flow to recruit alveoli in humans and a canine model of acute lung injury (ALI) but noted that the technique was crippled by CO₂ retention and acidosis.² In contrast, APRV couples the advantages of alveolar recruitment with chest wall elastic recoil to clear CO₂. Accordingly, APRV virtually eliminates neuromuscular blockade to facilitate ventilator management, reduces sedative needs, and supports cardiovascular performance while reducing pressor requirements.¹,³ These hemodynamic advantages augment regional blood flow during spontaneous ventilation,⁴,⁵ while recruiting and perfusing dependent (and usually atelectatic) lung.⁶

One must reconcile APRV’s seemingly vast ventilation volumes (release phase) with small volume ventilation (ARDSNet) in light of lung protection imperatives. Both strategies provide lung protection but in radically different fashions. ARDSNet avoids ventilating abnormal lung segments while awaiting underlying process resolution and pulmonary recovery. APRV deliberately recruits abnormal segments using lower pressures, spontaneous breathing, and long gas flow times to match disparate time constants. Recognizing that alveolar stretch and shearing forces promote biotrauma, APRV and ARDSNet both minimize these during intratidal ventilation. Rapid pressure change during APRV’s release phase might create shear stress, but that has yet to be substantiated. Further research needs to delineate APRV’s impact on pulmonary cytokine and chemokine elaboration.

Patients managed on APRV may also require operation. Although the trauma-intensivist may be comfortable with ARPV’s unique prescription, the anesthesiologist (especially one not specifically trained in critical care) may be acutely uncomfortable with the mode, the ventilator “knobology”, and maneuvers to correct hypoxia or hypercarbia. From a crisis management perspective, the operating surgeon should not be concomitantly managing the ventilator. A carefully implemented protocol addressing patient transport and intraoperative care is essential to ensure quality patient care and safety. Therefore, a multidiscipline strategy (surgery, anesthesia, critical care, respiratory therapy, and nursing) helps optimize patient care when using APRV.

There are defined patients for whom APRV is lifesaving (refractory hypoxemia), management benefiting (alveolar de-reRecruitment), and unnecessary (postoperative ventilation <24 hours). It is patients in the second group who merit additional attention as we delineate how APRV impacts resource utilization, nosocomial pneumonia, and duration of ventilation. Although most have lost their clinical equipoise regarding
inappropriate ventilator prescription and ALI, we have yet to explore implementing advanced ventilation methods such as APRV in the emergency department. The timely review by Dr. Seymour and colleagues should help us explore how to optimize ventilator strategies to support the trauma/critical care advances we regularly deploy in the intensive care unit and operating room.

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**REFERENCES**


**Erratum**

In Stein SC, Burnett MG, Glick HA. *Indications for CT scanning in mild traumatic brain injury: a cost-effectiveness study*. *J Trauma*. 2006;61:558–566. Table 2 was printed incorrectly. The correct table is below.

<table>
<thead>
<tr>
<th>GOS Score</th>
<th>Utility</th>
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GOS, Glasgow Outcome Score.