Airway Pressure Release Ventilation: What Do We Know?

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Airway pressure release ventilation (APRV) is inverse ratio, pressure controlled, intermittent mandatory ventilation with unrestricted spontaneous breathing. It is based on the principle of open lung approach. It has many purported advantages over conventional ventilation, including alveolar recruitment, improved oxygenation, preservation of spontaneous breathing, improved hemodynamics, and potential lung-protective effects. It has many claimed disadvantages related to risks of volutrauma, increased work of breathing, and increased energy expenditure related to spontaneous breathing. APRV is used mainly as a rescue therapy for the difficult to oxygenate patients with acute respiratory distress syndrome (ARDS). There is confusion regarding this mode of ventilation, due to the different terminology used in the literature. APRV settings include the “P high,” “T high,” “P low,” and “T low”. Physicians and respiratory therapists should be aware of the different ways and the rationales for setting these variables on the ventilators. Also, they should be familiar with the differences between APRV, biphasic positive airway pressure (BIPAP), and other conventional and nonconventional modes of ventilation. There is no solid proof that APRV improves mortality; however, there are ongoing studies that may reveal further information about this mode of ventilation. This paper reviews the different methods proposed for APRV settings, and summarizes the different studies comparing APRV and BIPAP, and the potential benefits and pitfalls for APRV.

Key words: airway pressure release ventilation; biphasic positive airway pressure; ARDS/ALI; ventilator-induced lung injury; acute respiratory failure. [Respir Care 2012;57(2):282–292. © 2012 Daedalus Enterprises]
Introduction

Airway pressure release ventilation (APRV) was first described and introduced to clinical practice over 20 years ago.1 It became commercially available in the mid-1990s.2 It is a mode of mechanical ventilation that is best described as a partial ventilatory support,3,4 and is based on the open lung concept.5,6 The primary goals of this mode were to provide both safety and comfort: safety in that adequate or superior ventilatory support is provided without dangerously high applied pressures, thus minimizing the risk of ventilator-induced lung injury (VILI), and without depressing hemodynamics, while comfort in that unrestricted spontaneous breathing would be allowed, which is a feature unavailable in conventional ventilatory modes, thus minimizing patient-ventilator asynchrony. Despite its theoretically attractive advantages over other conventional modes of ventilation, and its availability in most of the new commercially available ventilators, APRV is still not used routinely in clinical practice in North America. APRV is used more frequently in Europe.7 APRV is still mostly thought of as an alternative rescue mode for the difficult to oxygenate patient with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).8

Terminology

APRV is classified as pressure controlled intermittent mandatory ventilation, and is typically applied using inverse inspiratory-expiratory (I:E) ratios.9 As such, there are both mandatory breaths (ie, machine-triggered and machine-cycled), as well as spontaneous breaths (ie, patient-triggered and patient-cycled) (Fig. 1). The mandatory breaths applied by APRV are time-triggered, pressure-targeted, time-cycled breaths (depending on the ventilator, trigger and cycle events may be synchronized with patient breathing signals). Spontaneous breaths can occur both during and between mandatory breaths. Because APRV has historically been viewed as alternating levels of CPAP, the amplitude of the time-triggered mandatory breath is called “P high” instead of inspiratory pressure, and the duration is called “T high” instead of inspiratory time. Similarly, the expiratory pressure is called “P low” and the expiratory time (release time) is called “T low.”1,8,10

The confusion regarding this mode of ventilation arises from the different terminology used in the literature, as authors seldom provide adequately explicit definitions for the terms they use when describing various modes of ventilation.11 This issue has been studied by Rose and Hawkins,11 in an attempt to identify the definitional criteria of both APRV and biphasic positive airway pressure (BIPAP) modes. They concluded: “Ambiguity exists in the criteria that distinguish APRV and BIPAP.” The other source of confusion arises from the ventilator manufacturers’ choice of terminology. Different names have been coined for the same mode, such as BiLevel (Covidien), APRV (Dräger), Bi-Vent (Maquet), BiPhasic (CareFusion), and DuoPAP (Hamilton).

APRV Versus BIPAP

Both modes clearly have the same general pattern of airway pressures as intermittent mandatory ventilation, with time-triggered, pressure-targeted, and time-cycled mandatory breaths according to the preset values of T high and T low (Fig. 2). Both modes allow unrestricted spontaneous breathing both during and between mandatory breaths, but there is more time for them to occur during mandatory breaths with APRV. APRV typically uses extreme inverse I:E ratios, while BIPAP usually does not.11 Also APRV usually keeps the duration of the T low at ≤1.5 seconds, while there is no restriction on the T low in BIPAP.4,8,12
A recent review of 50 published studies of both modes\textsuperscript{11} showed that 78\% of the studies described APRV, while 22\% described BIPAP. Extreme inverse I:E (> 2:1) was used in 46\% of the studies describing APRV. None of the studies describing BIPAP used an I:E > 2:1. Twenty-one percent of the APRV studies used I:E of 1:1 to 2:1, compared to 9\% of studies describing BIPAP. Thirty-one percent of the APRV studies used I:E of 1:1, compared to 64\% of the BIPAP studies. Finally, only 5\% of the APRV studies used I:E less than 1:1, compared to 27\% of the BIPAP studies. The mean reported inspiratory time (T high) was 3.4 seconds for APRV, compared to 2.4 seconds for BIPAP. Conversely, the mean reported expiratory time (T low) was nearly 3 times longer in the BIPAP studies, compared to APRV (3.4 s and 1.3 s, respectively). The mean P high used in the APRV studies was 6 cm H\textsubscript{2}O higher, but not statistically significant, compared to the BIPAP studies.

Surprisingly, despite the difference in P high and T high settings, the mean P low was similar in both APRV and BIPAP, at 5.5 cm H\textsubscript{2}O.\textsuperscript{13}

Interestingly those 2 modes have never been compared head to head in an animal or human trial to determine if one is superior to the other. In a bench study using a lung simulator to compare both modes, with equivalent settings in an ARDS lung model, we found that APRV supplied higher mean airway pressure (P\textsubscript{aw}) but lower minute ventilation (V\textsubscript{E}) than BIPAP.\textsuperscript{14}

**APRV Versus Conventional Ventilation**

Several studies\textsuperscript{15–22} have compared APRV to conventional mechanical ventilation in humans with ALI/ARDS, but most of them are weakened by the small number of patients and by being short-term observations studies. Consistently, most of them have shown improvement in oxygenation, but none of them has shown mortality benefits in the APRV group. Putensen and colleagues\textsuperscript{18} randomized 30 trauma patients to either APRV or pressure-controlled continuous mandatory ventilation (PC-CMV); they have shown that the APRV group had shorter ventilator days (15 vs 21) and ICU days (23 vs 30). According to the authors, those findings were explained by the improvement in hemodynamics and the less sedation and no paralytic agents used in the APRV group. This study is weakened by the small number of patients (15 in each group), by the fact that only 20\% of the APRV group had ARDS, compared to 74\% in the PC-CMV group, and by the fact that the 2 groups had different sedation protocols. A recent retrospective study\textsuperscript{23} with a small number of patients, compared APRV to volume controlled intermittent mandatory ventilation (VC-IMV); beside improved oxygenation, it showed a trend to lower mortality in the APRV group, but did not reach statistical significance. A larger international retrospective study\textsuperscript{7} using propensity score to compare both APRV and BIPAP to conventional ventilation confirmed the significantly improved oxygenation with both modes, but failed to show any mortality benefits.

A recent study\textsuperscript{24} in 63 adult trauma patients requiring mechanical ventilation for greater than 72 hours showed that APRV has a similar safety profile as the low tidal volume ventilation. APRV patients tended to have increased ventilator days (10.49 \( \pm \) 7.23 d vs 8.00 \( \pm \) 4.01 d), ICU stay (16.47 \( \pm \) 12.83 d vs 14.18 \( \pm \) 13.26 d), and ventilator-associated pneumonia (VAP) (1.00 \( \pm \) 0.86 vs 0.56 \( \pm \) 0.67). This may be explained by the significant initial worse physiologic derangement demonstrated by Acute Physiology and Chronic Health Evaluation II (APACHE II) scores in the APRV group (20.5 \( \pm \) 5.35 vs 16.9 \( \pm \) 7.17).

**APRV Versus Other Non-Conventional Ventilation**

APRV shares some similar features with other non-conventional modes of ventilation (eg, inverse ratio ventilation, and high-frequency oscillatory ventilation [HFOV]).\textsuperscript{25–27} These modes attempt to improve oxygenation by increasing the mean P\textsubscript{aw}. Inverse ratio ventilation, either with volume or pressure control, increases the mean P\textsubscript{aw} through increasing the inspiratory time with I-E ratio more than 1:1. This causes patient discomfort, and heavy sedation or muscle paralytics may be required.\textsuperscript{26,27} HFOV also uses the open lung approach by applying very low tidal volume (potentially less than the anatomic dead space), using high-frequency oscillations around a high mean P\textsubscript{aw}.\textsuperscript{25} Heavy sedation and muscular blockers are usually required during HFOV in adults, due to the inability of the only commercially available device (in the United States) to accommodate spontaneous breathing adequately.\textsuperscript{28} A detailed description of those modes is beyond the scope of this review.

Table 1 highlights some of the differences between conventional ventilation (volume or pressure control), inverse
ratio ventilation (volume or pressure), BIPAP, APRV, and HFOV.

**APRV Settings**

As with any ventilation strategy in ARDS, the goal should be to ventilate the lung on the steep portion of the pressure-volume curve, where mean lung volume and pressures are adequate for oxygenation and ventilation, and the tidal volume lies between the lower and upper inflection points.6 This strategy has been found to improve lung compliance, venous admixture, and P\textsubscript{aO2} in ARDS, on one hand, and to protect the lung by avoiding either collapse during expiration (atelectrauma) or stretch injury during inspiration (volutrauma, barotrauma), both of which contribute to VILI.29–31

There has been no consensus in the literature in regard to setting APRV parameters, which continues to be a conundrum in clinical practice.32 We will discuss the various methods described and recommended in the literature for setting the P high/P low and the T high/T low, with their advantages and disadvantages. Of note, the most studied but the most difficult parameters to set were the P low and T low.33 There are generally 2 schools of thought, one advocating a short T low with a P low of zero cm H\textsubscript{2}O to prolong the inflation:deflation ratio and create auto-PEEP, while the other school is to use longer T low to eliminate the auto-PEEP and use a higher P low to avoid alveolar collapse. There are very few data to support either school of thought.8,32 In theory and mathematically (see Fig. 2) both strategies may be equivalent. In this review we will not make any recommendations on how to set the parameters, as there are no solid data to support them.

**P High/P Low**

Some authors4,12,18,34 recommended constructing a patient pressure-volume curve, and subsequently setting the P high below the upper inflection point (UIP), and the P low above the lower inflection point (LIP) of the inspiratory limb of the curve to avoid VILI. This method theoretically makes the most physiologic sense and has been studied extensively in conventional mechanical ventilation.35 However, clinicians are faced with the technical difficulties of obtaining a clear curve, and patients often have to be heavily sedated or paralyzed to obtain a passive breath.36 Moreover there is controversy in the literature regarding the benefits of this method in determining the optimal PEEP,37 as well as how to interpret the pressure-volume curves (ie, using the inspiratory38 or expiratory limb39 or the hysteresis of the curve40,41). New ventilators (eg, Hamilton G5 and Dräger Infinity) have integrated software tools that facilitate this task.

Other authors2,10,42 recommended setting the P high according to the plateau pressure of the volume controlled mode or the peak P\textsubscript{aw} of the pressure controlled mode. The general suggestion is to limit the P high to 30–35 cm H\textsubscript{2}O, while setting the P low at zero cm H\textsubscript{2}O in conjunction with setting a very short T low. The short T low creates intentional gas trapping (auto-PEEP) to maintain end-expiratory lung volume. This method takes into consideration avoiding excessive inflating pressures, but caution has to be exercised, taking into account that the resultant tidal volume might be highly variable and may be higher than the accepted standard of care (ie, 6–8 mL/kg)43 due to the contribution of the patient’s spontaneous inspiratory effort. The disadvantages of setting the P low empirically at zero cm H\textsubscript{2}O and depending on generating auto-PEEP to avoid lung collapse are that tidal volume cannot be

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**Table 1. Comparison of Conventional Ventilation, Inverse Ratio Ventilation, Biphasic Positive Airway Pressure, Airway Pressure Release Ventilation, and High-Frequency Oscillatory Ventilation**

<table>
<thead>
<tr>
<th></th>
<th>Conventional Ventilation</th>
<th>Inverse Ratio Ventilation</th>
<th>BIPAP</th>
<th>APRV</th>
<th>HFOV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:E ratio</td>
<td>1:4–1:1</td>
<td>&gt; 1:1</td>
<td>1:4–1:1</td>
<td>&gt; 2:1</td>
<td>1:2–1:3</td>
</tr>
<tr>
<td>Mean P\textsubscript{aw}</td>
<td>Less</td>
<td>Increased</td>
<td>Increased</td>
<td>Much Increased</td>
<td>Much Increased</td>
</tr>
<tr>
<td>Spontaneous breathing</td>
<td>Triggers a breath</td>
<td>Triggers a breath</td>
<td>Allowed at any time of the respiratory cycle</td>
<td>Allowed at any time of the respiratory cycle</td>
<td>Usually suppressed intentionally (can cause drop in mean P\textsubscript{aw})</td>
</tr>
<tr>
<td>Heavy sedation and Paralytics</td>
<td>May be required</td>
<td>Usually required</td>
<td>Not required</td>
<td>Not required</td>
<td>Usually required</td>
</tr>
<tr>
<td>Auto-PEEP</td>
<td>Less common</td>
<td>Common</td>
<td>Less common</td>
<td>Very common</td>
<td>Very common</td>
</tr>
</tbody>
</table>

BIPAP = biphasic positive airway pressure
APRV = airway pressure release ventilation
HFOV = high-frequency oscillatory ventilation
I:E ratio = inspiratory-expiratory ratio
P\textsubscript{aw} = airway pressure
controlled independently of end-expiratory lung volume (as with conventional ventilation) and that even small changes in lung mechanics cause large changes in both variables. Auto-PEEP may be highly variable and an unreliable way of avoiding alveolar collapse in contrast to applied PEEP.8,44,45

Other authors1 have set the P high and P low according to oxygenation and ventilation parameters. This method is totally empirical and discouraged, as it does not take into account lung volumes or pressures.

Newer research46 has looked into titrating the P low to achieve a protective tidal volume of 4–6 mL/kg, in compliance with the ARDS Network recommendations.43 This method is difficult to achieve in the spontaneously breathing patient, as the effects on the tidal volume during the releases will be variable.

**T High/T Low**

Most authors focus on the setting of T low and leave T high as a function of the overall desired frequency of mandatory breaths (usually 8–12 breaths/min).

Some authors2–10 have advocated setting the T low according to the expiratory flow curve decay to achieve about 50% of peak expiratory flow as a way to achieve auto-PEEP and avoid lung collapse. This method attempts to create an expected average amount of auto-PEEP. The problem with that method is that the amount of auto-PEEP generated is highly variable and depends on the set P high (assuming P low = 0 cm H2O), respiratory system elastance, and resistance, all of which change frequently during mechanical ventilation. More importantly, this is a difficult task to achieve at the bedside8,32 and the actual level of auto-PEEP is also difficult to measure with most ventilators (Fig. 3). New technology might help facilitate setting T low by allowing the trigger for mandatory breaths to be set as a percentage of the peak expiratory flow, a feature available on the Dräger Infinity ventilator (Auto Release feature).

Others have advocated setting the T low according to the expiratory time constant (τ) of the respiratory system.10,31 The time constant is calculated as the product of the static respiratory compliance and resistance, both of which are easily obtained at the bedside. This method allows a theoretical estimate of the amount of auto-PEEP generated (Fig. 4). Pressure, volume, and flow all decay according to the same time constant (assuming a simple, single-compartment model of the respiratory system). During each time constant, each variable changes by 63.2%.

Thus, for example, after one time constant, alveolar pressure is 36.8% of its initial value; after 2 time constants it is 13.5%, after 3 time constants it is 5%, and after 4 time constants it is 1.8%. Therefore, if the P high is 30 cm H2O, P low is 0 cm H2O, and the T low is set at one time constant, then the expected auto-PEEP is about 11 cm H2O, 4 cm H2O at 2 time constants, 1.5 cm H2O at 3 time constants, and so on theoretically till infinity if no breath follows. Usually 4–5 times the expiratory time constant is needed to eliminate auto-PEEP.31,36 Unfortunately, such estimation has been shown to be very inaccurate, probably due to the fact that the model does not account for the effect on the time constant of the mechanical properties of the expiratory limb of different ventilators45 (Fig. 5). Caution has to be exercised, as the time constant changes frequently during mechanical ventilation and a guaranteed alveolar pressure may not be maintained.9 Another concern is that even with very short T low, alveolar derecruitment may occur.47 Nevertheless, in a neonatal sheep model of ARDS, Martin and Wetzel48 found that release times of 2–3 time constants maintained adequate oxygenation and ventilation. Another study, by Neumann and colleagues,49 has shown that T low less than 1.5 seconds has resulted in lower tidal volumes, but the Ve was maintained, with the parallel increase of spontaneous respiratory rate.

Some authors2,10 have published guidelines for the initial settings of APRV, and they recommended a T low range of 0.2–0.8 seconds. Setting the T low as high as 0.8 seconds in ARDS, whose time constant is usually very short, may cause alveolar collapse and derecruitment, which might be dangerous, especially if the P low used is zero cm H2O.

Earlier studies1 have used empirical settings of T low directly and T high indirectly (by the frequency of releases or mandatory breaths) to achieve certain oxygenation and ventilation end points. Again, this is discouraged, as it does not take into account the resultant tidal volume and risk of stretch damage to the lungs.2–30

**Fig. 3. Lung simulator diagram of airway pressure release ventilation (APRV); volume (yellow), lung pressure (white), and flow (orange)/time curve. Time constant (TC) was known and the T low was set to more than 4 TCs. The blue vertical lines represent each TC. Intrinsic PEEP at each TC would be equal to the point intersecting with the pressure curve, or can be calculated as the end-expiratory lung volume divided by respiratory compliance. Notice that at each TC the flow curve did not decay to 36.2% from its previous value, as expected per the mathematical model.**
Others have looked at titrating the T low to achieve certain predefined protective tidal volume. Conceptually, this method tries to accomplish a protective lung strategy. Unfortunately, the tidal volume will vary with patients’ efforts, and changes in lung mechanics.

Settings Adjuncts

Pressure Support and Automatic Tube Compensation

Most of current commercially available ventilators have incorporated the addition of pressure support (PS) and automatic tube compensation (ATC) to augment the patient’s spontaneous breaths or to overcome the artificial airway resistance. Experts have expressed their concerns about those adjuncts because the additional elevation of applied pressures may significantly raise the transpulmonary pressure above safe levels, contributing to VILI when the assist is delivered during the P high. Additionally, that support may eliminate the transient drop in transpulmonary pressure created by unassisted spontaneous breaths and thus obviate their putative beneficial effects.

Synchronization

Some ventilator manufacturers have incorporated a synchronization interface for switching from P high to P low, and vice versa, according to the patient’s spontaneous breaths, to avoid patient-ventilator asynchrony. Usually a synchronization window of 0.25–0.3 seconds is used for both triggering and cycling of the mandatory breaths. The benefits from such a strategy have not been reported.

APRV and Weaning

Some authors have described a “drop and stretch method” of weaning APRV; they gradually reduced the level of P high (“drop”) and reduced the number of releases by increasing the T high (“stretch”) until the mode is converted to CPAP as a method of spontaneous breathing trial before extubation. A study by Rathgeber and colleagues compared duration of weaning between BIPAP, VC-IMV, and volume controlled continuous mandatory ventilation (VC-CMV) in postoperative cardiac patients, and reported a small yet significant reduction in time on mechanical ventilation. To our knowledge there are no
published studies comparing APRV to conventional weaning methods like pressure support ventilation (PSV) or T-tube, or to newer closed loop ventilation methods such as ATC, proportional assist ventilation (PAV), adaptive support ventilation (ASV), or Smart Care.

Advantages of APRV

APRV is considered an “open lung approach,” a concept of maximizing and maintaining alveolar recruitment throughout the ventilatory cycle by potentially ventilating the lung on the steep portion of the pressure-volume curve, thus avoiding over-distention on inspiration and alveolar collapse on exhalation. Its major advantages over other modes of conventional ventilation are the preservation of spontaneous unassisted ventilation throughout the entire ventilatory cycle, maintenance of relatively long inflation time, and potential lung-protective benefits.

Spontaneous Ventilation

Spontaneous breathing, accounting for 10–30% of $V_E$ during APRV, leads to improved ventilation-perfusion matching, decreased intrapulmonary shunt, and decreased dead space, through improvement of transpulmonary pressure in the juxtadiaphragmatic lung regions, with alveolar recruitment, and without raising peak $P_{aw}$. This is in contrast with conventional ventilation, which leads to alteration of normal ventilation distribution and atelectasis in dependent lung areas. Furthermore, regular spontaneous breathing maintains diaphragmatic muscle condition. Putensen and colleagues have documented the benefits of spontaneous breathing during APRV, which has increased the respiratory-system compliance, $P_{ao2}$, cardiac index, and oxygen delivery, compared to patients who were paralyzed during mechanical ventilation.

Froese and colleagues showed that about 60% of the diaphragmatic movements occur in the most dependent regions of the lungs during spontaneous breathing in supine patients, in contrast to 10% movement in paralyzed patients on mechanical ventilation. A surprising finding was that, despite the spontaneous breathing, the WOB and oxygen consumption on APRV were not affected.

Another major benefit of spontaneous breathing during APRV is the resulting improved patient comfort. Patients have the ability to maintain their spontaneous tidal volumes with an unrestricted flow pattern. The patient has the ability to adjust their spontaneous ventilation in relation to their metabolic needs, which translates in better synchrony with the ventilator, improving comfort, leading to a reduced need for sedation. Studies have reported up to 70% reduction in the use of neuromuscular blocking agents (NMBAs) and 40% reduction in sedation requirements, compared to conventional ventilation. The use of sedation leads to depression of cough reflex and increased risk of aspiration of pharyngeal secretions. Unrestricted spontaneous breathing allows the patient to cough during mandatory breaths, contributing to secretion clearance and possibly reducing the risk of VAP, which can translate to the potential for decreasing the duration of ventilation. A recent study has shown that APRV reduces the risk of VAP in trauma patients with pulmonary contusion.

The increase in cardiac output related to spontaneous breathing is due to the decrease of pleural pressure and increase of abdominal pressure. Thus, blood is shifted from abdominal viscera to inferior vena cava, where the venous return to the heart is increased. Suppression of spontaneous breathing during conventional ventilation can compromise cardiovascular function by decreasing venous return and thus the cardiac output. Studies in medical and trauma patients comparing APRV to conventional ventilation have shown increased cardiac index and oxygen delivery in patients on APRV. However, other studies have shown no significant difference in hemodynamics between APRV and conventional ventilation. Some animal studies have shown increased regional blood flow and increased perfusion to cerebral, renal, hepatic, and splanchnic circulation while on APRV. Some studies indicate that APRV does not compromise circulatory function and tissue oxygenation, whereas conventional ventilation can impair cardiovascular function significantly.

Long Inflation Time

The benefit of a prolonged inflation time can be appreciated when we consider the uneven distribution of lung pathology in ALI/ARDS. The main causes of hypoxemia in ALI/ARDS are shunting due to alveolar collapse and reduction in functional residual capacity. Lung units with reduced compliance have short time constants, thus inflating and deflating slowly. Lung units with normal compliance have relatively long time constants, thus inflating and deflating slowly. A prolonged $T_h$ is presumed to achieve the treatment goal of alveolar recruitment because it allows time for slow lung units in a non-homogenous lung field to inflate. Furthermore, longer inflation times promote collateral ventilation through the channels of Martin, the pores of Kohn, and the canals of Lambert. Thus, the longer the inflation time, the greater the lung areas potentially available for gas exchange. The higher mean $P_{aw}$ created with $T_h$ and short $T_l$ settings presumably results in higher mean lung volumes. To attain the same mean $P_{aw}$ with conventional volume controlled ventilation requires either larger tidal volume with the higher risk of volutrauma, prolonged inspiratory time as in inverse ratio ventilation that usually requires high levels of sedation along with the risk of hemodynamic compromise and auto-PEEP.
respiratory rate with the risk of VILI secondary to cyclical alveolar opening and collapsing, or the addition of higher levels of PEEP. Such strategy had been a matter of debate for a long time. Three recent trials have documented improved oxygenation with higher PEEP, but no survival advantages, compared to lower PEEP levels.

Longer inflation times allow a greater probability of spontaneous breaths during T high. Animal and human studies with ALI have shown that allowing spontaneous breathing improved ventilation-perfusion matching by a marked decrease of intrapulmonary shunt.

The long inflation time allows using lower peak $P_{aw}$, and hence tidal volumes, to maintain mean $P_{aw}$. Studies in patients with ALI/ARDS have shown that APRV allowed a 17% reduction in peak $P_{aw}$ compared with conventional volume controlled ventilation adjusted to deliver a comparable or lower ventilatory support.

Lung-Protective Benefits

The potential lung-protective benefit of APRV depends on judicious selection of settings to ensure ventilation on the advantageous portion of the pressure-volume curve. A small study of 19 patients by Patel and colleagues comparing APRV to low tidal volume (ARDSNet) ventilation in ALI showed comparable safety and outcomes using both strategies. Moreover the long inflation time results in less frequent inflation and deflation, which can contribute to shear stress on the alveoli. A recent animal study showed that APRV decreases bronchoalveolar lavage fluid high-mobility group box-1 levels and lung water, compared to low tidal volume ventilation, signifying a decreased risk for VILI. However the relationship between APRV and VILI is more theoretical and has not been well studied or documented.

APRV and Mortality

No reported studies have shown improved mortality with APRV use. One small retrospective study of 58 patients has shown a trend toward mortality benefit: 31% in the APRV group, compared to 59% in the SIMV group ($P$ value of .05).

Disadvantages of APRV

Spontaneous Breathing

APRV is a mode of ventilation that has its own limitations. There are some worries regarding the spontaneous breathing during APRV. Field and colleagues reported that spontaneous breathing efforts can result in increased oxygen consumption by the respiratory muscles, which may exceed 25% of total body oxygen consumption. This was a small, uncontrolled study and done using conventional ventilation. Uyar and colleagues studied energy expenditure between APRV and PSV in a crossover study in patients without substantial lung disease and found no significant differences between both modes. In an animal model, the perfusion of the diaphragm, external intercostals and expiratory muscles increased by 2,500%, 900%, and 300% during spontaneous breathing, respectively. The increased perfusion of respiratory muscle may drive systemic perfusion and oxygen delivery away from vital organs, which can be deleterious, especially in shock states. It is well known that hypoperfusion of the gastrointestinal tract facilitates translocation of bacteria into the systemic circulation.

Work of Breathing

The timing of spontaneous breathing during the APRV cycle can have significant effect on the amount of work of breathing (WOB). Breaths that occur at the P low or during the pressure-release transition from the P high to P low have higher WOB. Additionally, those breaths may create the most discomfort and asynchrony, as $P_{aw}$ would be decreasing and gas flow would be escaping the circuit just as the patient was trying to inspire. This might be an argument in favor of synchronizing mandatory breathing with a spontaneous expiration during T high. On the other hand, spontaneous breaths occurring during the P high should have the least amount of WOB, unless an excessive level of pressure is used, causing lung over-distention that paradoxically increases the elastic WOB.

The breathing efforts may increase the transcapillary pressure gradient, thus enhancing pulmonary edema formation. The impact of spontaneous breathing on pulmonary edema formation during APRV is potentially dependent upon the P high level and the I-E ratio employed. However, APRV is not the only mode of ventilation associated with substantial respiratory efforts. Vigorous inspiratory efforts usually occur during conventional volume or pressure control modes, especially with lung-protective ventilation, to meet the metabolic demands. Thus, these modes may accentuate pulmonary edema formation too. Other limitations of APRV are related to the $V_{E}$. APRV relies on the small number of respiratory cycles to create the high inflation time and the higher mean $P_{aw}$. However, this limited number of cycles per minute has to create the baseline $V_{E}$. This means that a substantial amount of $V_{E}$ (occasionally up to 70% of the $V_{E}$ demand) may be abruptly shifted to the patient. This could result in an acute rise in $P_{ACO2}$ level and a marked increase in respiratory drive and WOB. Thus, the potential options to decrease WOB while maintaining $V_{E}$ are to decrease the time ratios (T high: T low), or to increase the cycle frequency or to increase the mandatory breath volumes. Decreasing the time ra-
usually maintains both the mandatory $V_E$ and the lung-protective ventilation. On the other hand, the high inflation time and oxygenation can be potentially sacrificed. In some studies the cycle ratio reached 1:1.78

**Tidal Volume and Minute Ventilation**

APRV, as a form of pressure controlled ventilation, carries the risk of volume changes with alteration in lung mechanics and the changes in the patient’s spontaneous inspiratory effort, which may cause large tidal volume and transpulmonary pressure swings, potentially contributing to volutrauma.30,32 Larger release volumes could maintain $V_E$, and this would produce a more satisfying breath while lessening the power demands on the respiratory muscles.

In some APRV studies the measured exhaled volumes were 9 mL/kg of measured body weight.19,78 We have personally observed exhaled volumes considerably larger than this. Large exhaled volumes imply potentially large end-inspiratory volumes that might obviate the desired lung-protective strategies, with potential increase in VILI and possibly mortality.86 Thus, the theory that the superimposition of spontaneous tidal volumes on the top of the mandatory breath may increase the likelihood of stretch-related injury is in question.32,84

There is a concern that patients with left ventricular dysfunction may not benefit from the augmentation of venous return and the increase in afterload occurring with the decrease in intrathoracic pressures.55 There is also the theoretical concern for using APRV in patients with COPD who require prolonged exhalation time, though there are no conclusive data.8,10 The limited research and experience with this form of ventilation can be a potential problem in certain facilities, though this mode is now integrated on most new commercially used ventilators.

**Present and Future**

The lack of proven mortality reduction has been a factor in the slow adoption of this mode, but there is an increasing interest. There are ongoing studies registered in the National Institutes of Health (clinicaltrials.gov), mostly comparing APRV to low tidal volume ventilation as a lung-protective strategy, which hopefully may shed more light on this mode and answer some of the needed questions.

**Conclusions**

Despite increasing evidence of improving oxygenation, hemodynamics, patient comfort, and safety, there are still a lot of unanswered questions regarding this unconventional mode of ventilation. In the United States the lack of proof that APRV in ALI/ARDS improves mortality has kept this mode in the shadows as a primary ventilatory mode, and it is only thought of as a rescue therapy for the difficult to oxygenate patient. More work and well organized studies seem prudent for the continued use and the acceptance of APRV in day-to-day clinical practice.

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