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Review Article

Airway Pressure Release Ventilation (APRV) Ventilator Mode in ICU

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Background

Airway pressure release ventilation (APRV) was first introduced in 1987 by Downs and Stock. It was developed as a lung-protective mode allowing for constant recruitment of alveoli, while minimizing ventilator-induced lung injury [1,2]. This method of ventilation provides increased airway pressure for an extended period of time with a momentary release, allowing for recoil of the lung producing a tidal volume relative to its elastic properties [3]. In essence, it is a continuous positive airway pressure therapy (CPAP) with a release phase allowing spontaneous breathing which provides potential benefits of decreased sedation, shorter duration of mechanical ventilation, and improvement in cardiac performance [4]. With no spontaneous breaths, APRV simply becomes an inverse inspiratory expiratory ratio (I: E) pressure controlled time cycled ventilatory mode. Its performance however is dependent on the operator selected [5]. Although it has not shown benefit in mortality, its effect on improving oxygenation with lung protective strategy is gaining popularity [6,7].

APRV has been implemented in various mechanical ventilators; however this mode may have different names depending on the company's ventilator (Table 1).

Ventilator Company	Mode
Dräger®	APRV
Servo-i®	Bi-Vent
Puritan Bennett™ 840	Bi-Level
Hamilton	DuoPAP+

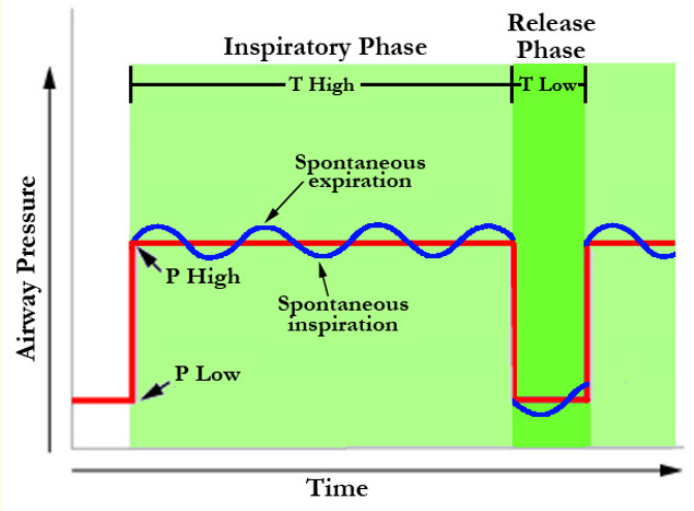
Table 1: *Various ventilator companies and their analogous modes to APRV.*

The primary aim of this systemic review is to discuss the mechanism of APRV ventilator mode, its indications, effects and comparison to the conventional strategies by reviewing the published literature. We reviewed articles where APRV was studied and situations where APRV may or may not be indicated.

Mechanism of APRV Mode

APRV is an application of CPAP with an extended inspiratory time to recruit alveoli with an intermittent release phase from high pressure (P High) to the lower pressure (P Low) resulting in removal of carbon dioxide (CO_2) (Figure 1). These unique properties allow a patient to spontaneously breathe at any time of the respiratory cycle, maintaining the natural course of breathing with an optimal functional residual capacity (FRC). It is a time cycled mode that allows constant alveolar recruitment with the expense of high mean

airway pressures, while decreasing the risk of ventilator induced lung injury (VILI) by avoiding repeated inflation and deflation [8,9]. At the beginning of T High, there will be an initial high flow, which will then zero, but on release at T Low, the flow will be expiratory, but will not zero because the time is to short, allowing the auto-positive end expiratory pressure (PEEP) (Figure 2).



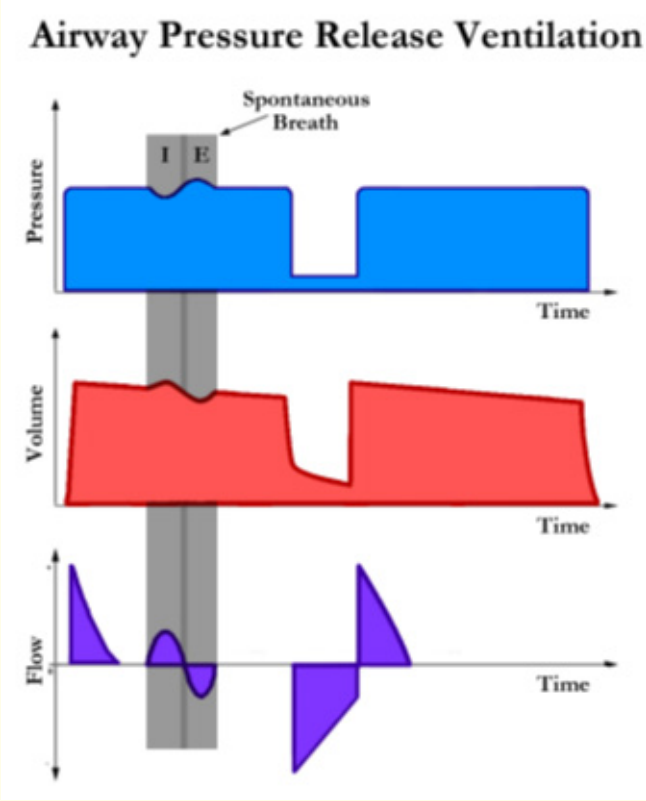


Figure 1 and 2: *Mechanism of APRV showing CPAP with an extended inspiratory time with an intermittent release phase from high pressure (P High) to the lower pressure (P Low) with spontaneous breaths in between.*

Effects on oxygenation

Studies have shown beneficial effects of APRV in regards to oxygenation in ARDS [10,11]. Better oxygenation results from constant alveolar recruitment is achieved due to constant high pressures [12]. The spontaneous respirations causing greater displacement of the lower diaphragm and recruited alveoli lead to proper gas distribution and improvement in ventilation and perfusion (V/Q) matching [13,14]. Moreover, not only better gas exchange, but improved compliance of the lung and decrease work of the breathing is noted, which again contribute to improved oxygenation (Figure 3).

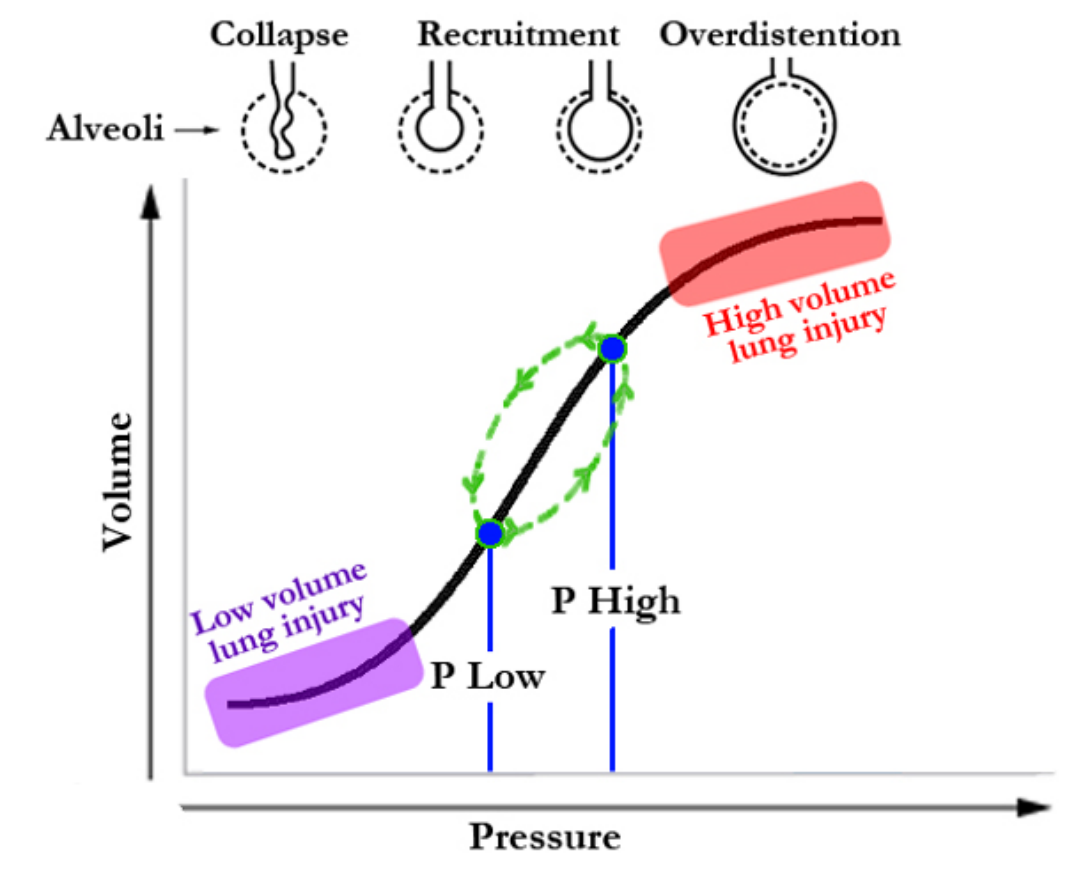


Figure 3: *Association of APRV with compliance of the alveoli and risk of VILI.*

When compared to pressure support ventilation (PSV), APRV demonstrated better oxygenation and lung aeration, suggesting a decrease in atelectasis and improvement in V/Q mismatching [15]. Maung and colleagues transitioned their patients to APRV once oxygen requirements were higher than 90%. They found hypoxemia was corrected in less than 10 minutes in the majority of their cases [16]. APRV has shown to be useful in post-surgical patients who often have atelectasis due to pain [10]. Also this mode has shown to improve oxygenation in morbidly obese patients who have poor lung function with low lung volumes and compliance [17]. APRV has shown to increase cardiac function, leading to improved oxygenation [18,19].

Effects on ventilation

Minute ventilation and removal of CO_2 in APRV depends on various factors including lung compliance, airway resistance, magnitude and duration of pressure release, and patient's spontaneous breathing [13,20,21]. Immediately after starting APRV, hypercarbia is often appreciated due to a brief release of high pressure to low pressure, resulting in breath stacking. As APRV is continued, CO_2 levels later decline toward target values [16]. If hypercarbia persist, the ventilator settings can be adjusted by either reducing the time in P High (T High) or increasing the time in P Low (T Low). This allows more time for exhalation and ultimately improves hypercarbia. When compared to CPAP alone, APRV has shown to provide better CO_2 clearance [4]. Although there have been studies showing improved ventilation on APRV, due to an initial hypercapnic state upon starting this mode, it has not been well studied in chronic obstructive pulmonary disease (COPD) patients. However there have been case reports showing improvements in hypercapnia when APRV was used after failure of other ventilatory modes [22].

Effect on cardiac physiology

A patient's spontaneous respiratory effort during APRV mode is thought to improve cardiac function [18,19]. A study by Putensen and colleagues, compared APRV versus pressure support ventilator (PSV), a form of ventilation that involves spontaneous breaths, where they found an increase in right ventricular end diastolic volume index (RVEDVI), right ventricular ejection fraction (RVEF) and cardiac index (CI) during spontaneous respiration in APRV [5]. Their findings support the concept that a fall in intrathoracic pressure during spontaneous inspiration may improve venous return and cardiac output [23]. Compatible with previous studies during intermittent mandatory ventilation increase in RVEDVI, RVEF, and CI was highest during unassisted spontaneous breathing with APRV. Their rationale was explained by spontaneous breathing with diaphragmatic contractions leading to a better distribution of ventilation to dependent lung areas causing improved V/Q matching [24].

Ultimately, increase in cardiac output may support the perfusion of nondependent high V/Q mismatch spaces and dead space regions [10]. It is also known that mechanical cycles increase ventilation in already well ventilated and poorly perfused lung areas [10,24]. Similarly, spontaneous breaths during APRV may have contributed to improved V/Q matching and decreased dead space ventilation in the presence of ARDS. The results of this study demonstrate that uncoupling of spontaneous and mechanical breaths during APRV contributes to improve V/Q matching and increased systemic blood flow in patients with severe ARDS.

Extended CPAP is one of the main modalities of APRV causing better gas exchange and when spontaneous respirations are added to this mix, it leads to better recruitment of alveoli, a subsequent decrease in hypoxic pulmonary vasoconstriction and a decrease in pulmonary pressures, leading to an increase in RVEF, cardiac output and, increased overall oxygen delivery [16]. Walsh., *et al.* showed APRV improved pulmonary blood flow, cardiac output and oxygen delivery in pediatric patients who had congenital heart defects status post repair of either tetralogy of Fallot or cavopulmonary shunts [18]. There is data from animal studies that required less use of a vasopressor and better mean arterial pressure (MAP) control in the APRV group as compared to low tidal volume groups in ARDS [3].

Effect on organ perfusion

APRV has been shown to increase organ perfusion in many animal studies. Hering., *et al.* showed APRV improved blood flow to respiratory muscles, stomach, duodenum, ileum and colon in 12 pigs with acute lung injury (ALI) [24,25]. Kaplan., *et al.* found that patients on APRV had improved urine output and glomerular filtration rate when compared to pressure control ventilation (PCV) [26]. These improvements in renal blood flow and glomerular filtration are again thought to be associated with spontaneous breathing during CPAP, which is thought to increase preload, improve cardiac index with subsequent improvement in arterial blood oxygenation and systemic blood flow [27].

Sedation using APRV mode

Sedatives, analgesics, and neuromuscular blocking agents are commonly used in the intensive care unit (ICU) and are associated with adverse outcomes such as an increased risk of ventilator associated pneumonia (VAP), duration of ventilation and ICU days [28-30]. Given ARPV requires the patient to breath spontaneously, and the level of sedation must be minimal. When using APRV, a Richmond Agitation Sedation Scale (RASS) score between 0 - 3 should be targeted [13]. Studies on APRV and sedation have shown to decrease the need for neuromuscular blockade use by 70% and the use of sedation by 40% compared to PCV [6,31]. As a result, the mode may be associated with decreased sedation and analgesia medications which in turn improve sedation status compared to other ventilation methods [32].

Comparison with different ventilator modes

Many studies have been performed comparing APRV to more traditional modes of ventilation; however APRV has shown no difference in mortality.[2] Nonetheless, promising results from APRV have been seen regularly. It has been shown that by stabilizing and recruiting maximum alveoli while minimizing over distention and collapse, it may reduce the incidence of ARDS and protect the injured lung (Figure 3) [33,34]. To reduce the incidence of ARDS the mode should theoretically be started in patients who have a ratio of arterial oxygen partial pressure to fractional inspired oxygen ($Pa0_2/Fi0_2$) > 300 millimeters of mercury (mm Hg). Animal studies have shown that APRV can prevent ARDS more compared of LTV ventilation when $Pa0_2/Fi0_2$ > 300, which demonstrates APRV can be used not only for treatment of ARDS develops but also as preventive strategy [3]. Li., *et al.* showed that APRV in patients with ARDS and $Pa0_2/Fi0_2$ < 200 mmHg improved oxygenation up to 48 hours. However, there was no difference after the 48 hour mark in regarding improved oxygenation. At the same time, peak pressures were reduced and FRC was enhanced. The number of days on sedation were significantly reduced in the APRV group while days without mechanical ventilation were increased and days in ICU were shortened significantly [35]. Walkey and colleagues found the rate of ventilator associated pneumonia was reduced when using APRV compared with volume assist control [36].

It is well known that low tidal volume (LTV) ventilation improves mortality in patients with ARDS [37]. Subsequently, it was shown that LTV also decreases serum inflammatory marker interleukin- 6 (IL-6) [38]. In an animal study APRV use was associated with lower bronchoalveolar lavage IL-6 as compared to low tidal volume ventilation in ARDS [39].

Tolerance of APRV mode

It is thought that spontaneous breathing in APRV provides better patient-ventilator synchrony leading to improved patient comfort [40]. Optimal V/Q matching occurs by promoting more physiological gas distribution to the non-dependent regions of the lung [10,11,41,42]. In contrast to this, Shipley and colleagues demonstrated, theoretically, APRV provides better synchrony by allowing the patient to take breaths at any moment. When spontaneous breaths are taken during P High, it can generate higher tidal volumes in comparison to standard pressure or volume control modes [43]. Increased tidal volumes causes high risk of pneumothorax, high right ventricle overload which can eventually cause increases in intrathoracic pressures, later leading to decrease venous return and a decrease in cardiac output. These disadvantages are contrary to what APRV is known for. Since spontaneous breath may occur during any phase of the respiratory cycle, this can cause variable tidal volumes from 180 - 790 milliliters (ml) which may lead to increase transpulmonary pressure (TPP) [TPP: alveolar pressure minus PEEP], further increasing risk of VILI [16,44].

APRV as a rescue therapy in ARDS

In patients who have moderate to severe ARDS, APRV is usually only considered as a rescue therapy after paralysis, deep sedation, high PEEP or proning have failed to correct hypoxemia [44]. Early paralysis is common practice in moderate to severe ARDS patients [45]. However, initiation of paralysis during APRV results in no spontaneous breaths which are analogous to PCV. It is still unknown whether to paralyze a patient versus starting APRV without paralytics for early ARDS. Future studies are needed to constitute the approach. It is well known that once APRV is initiated, sedation needs to be minimized and patients need to be off chemical paralysis in order to breathe spontaneously.

When to use APRV mode

In the literature thus far, there is no clear indication of when to start APRV. APRV should be considered in ARDS patients with $Fi0_2$ more than 50% and requiring PEEP of more than 10 mmHg [2]. Studies were mostly done in patients with moderate to severe ARDS, post-surgical and post- trauma [10] It also may have utility in pregnant patients who suffer from ARDS [46,47]. APRV in refractory hypoxemia has been described in small studies and case reports [48]. However, to the best of our knowledge, there are only few randomized control trials comparing APRV to different modes for refractory hypoxemia. Putensen., *et al.* compared APRV and PCV and demonstrated that APRV was associated with improved arterial oxygenation [10]. Varpula., *et al.* compared APRV and synchronized intermittent mandatory ventilation (SIMV) with pressure support and found significant improvement in oxygenation while using APRV, more so when used with prone positioning. They concluded that the use of pruning while on ARPV mode compared to pruning while on SIMV lead to better oxygenation explained by increased in $Pa0_2/Fi0_2$. This study showed that the prone position along with spontaneous breaths with APRV had synergistic effects leading to improved oxygenation in ARDS patients. There was no mortality benefit by either study [49].

When not to use APRV mode

Spontaneous breathing is the main entity in APRV which warrants minimal sedation. APRV should not be used in patients who require deep sedation for management of their underlying disease (e.g. cerebral edema with increased intracranial pressure (ICP) or status epilepticus) as being sedated would render them unable to spontaneously breathe, thus losing the potential benefits of ARPV [21]. APRV should also be avoided in disease states where mean airway pressures (MAP) are increased e.g. increased ICP or large bronchopleural fistulas as MAP can be worsened during spontaneous respirations and P high [2]. Historically; clinicians have been reluctant to use APRV in patients with traumatic brain injury (TBI) due to higher MAP causing increasing ICP [50]. Even with this reluctance, there have been cases and studies which did demonstrate promise in cases with TBI and the use of APRV. These studies showed evidence against conventional thought regarding ventilation and intracranial pressures. Normally in states of increase ICP, hyperventilation is the basis of treatment which causes a subsequent decrease in ICP. Fletcher and colleagues found that when using APRV, there is an increase in cerebral blood flow possibly secondary to increased cardiac output without a consequent increase in ICP, the explanation of which is unknown [51,52]. There is minimal data available on the use of APRV in patients with obstructive lung disease including asthma and COPD. These disease states are associated with hypercapnia and the use of APRV at least in the initial setting causes an increase in CO_2. COPD and asthma are relative contraindications to using APRV because of potential hypercapnia as well as requirements of longer expiratory times needed for increased ventilation and CO_2 washout. Even with this relative contraindication there are some reports where APRV was successful in treating this disorders [6,53]. Like COPD and asthma, use of APRV has not been investigated thoroughly in patients with neuromuscular disease [13].

There are complications associated with APRV use in patients with right ventricular overload. APRV should be reconsidered in patients with elevated pulmonary pressures given increased intrathoracic pressures leading to decrease venous return and poor cardiac output [44,54].

Complications

APRV has gained popularity recently due to its lung protective strategy by decreasing repetitive inflation and deflation of the alveoli, better oxygenation, ventilation and hemodynamics. However, the mode is not universally applied. Adequate on-site training, coupled with off-site support services will help resolve some of the stress and decrease the risks associated with APRV [55]. There is conflicting data with regards to the advantages and disadvantages of using APRV. Some studies involving trauma patients using APRV actually increased ventilator days compared to other modes of ventilation [45,56]. Though most literature states that APRV is comfortable for the patient, it is a mode that is time-cycled and synchrony with the patient's spontaneous respiration may not actually occur. If the release phase is not synchronous with the patient's effort, desynchrony may result, deeming it an inappropriate mode of ventilation [57]. Other cases

demonstrate that intravascular volume often needs to be augmented in patients on APRV to offset the decrease in venous return to the heart, which occurs due to prolonged positive intrathoracic pressures, resulting in decreased cardiac output [55]. This contradicts other studies that show increase in cardiac output by increases in venous return. APRV can also carry a small risk of pneumothorax [16]. Auto-positive end expiratory pressure (PEEP) is also a concerning factor when using APRV. Due to short exhalation times in this mode, there is a risk for increase in auto-PEEP. This occurs when exhalation time terminates before equilibrium between airway and alveolar pressure and when the end expiratory flow persists. When this occurs, total PEEP exceeds the set point in which hyperinflation occurs and the consequence of this include hypotension, decreases in ventilation, and hypoxemia [57].

APRV is suitable for ventilator weaning, though its superiority to conventional modes, e.g. pressure support ventilation, has not been demonstrated at this time [6,57].

Conclusion

APRV has recently gained traction in the ICU, especially in ARDS patients to improve oxygenation with better hemodynamic profiles and reducing lung injury. Strict indications to initiate APRV is still in question, but it is well known that an early initiation does no harm and improves outcomes in animal studies [3]. Less use of sedation will perpetually decrease delirium, which improves mortality ICU patients [58]. It has been noted to be more comfortable than other modes of ventilation because of spontaneous breathing, allowing better patient ventilator synchrony. The theoretical advantage to the mode is its ability to maximize alveoli recruitment by maintaining a higher constant CPAP, while the peak inspiratory pressure remains lower than conventional ventilation [2]. Though most studies have shown improvement in oxygenation in patients on APRV versus conventional ventilation, none have shown a decrease in mortality [2,6]. More studies are required involving diverse disease states for making APRV a conventional mode in regular ICU practice.

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