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# Airway Pressure Release Ventilation for lung protection in acute respiratory distress syndrome: an alternative way to recruit the lungs

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**ABSTRACT**

***Purpose of review**:* Airway pressure release ventilation (APRV) is a modality of ventilation in which high inspiratory continuous positive airway pressure (CPAP) alternates with brief releases. In this review, we will discuss the rationale for APRV as a lung protective strategy and then provide a practical introduction to initiating APRV using the *time-controlled adaptive ventilation (TCAV)* method.

***Recent findings**:* APRV using the TCAV method uses an extended inspiratory time and brief expiratory release to first stabilize and then gradually recruit collapsed lung (over hours/days), by progressively 'ratcheting' open a small volume of collapsed tissue with each breath. The brief expiratory release acts as a 'brake' preventing newly recruited units from re-collapsing, reversing the main drivers of ventilator-induced lung injury (VILI). The precise timing of each release is based on analysis of expiratory flow and is set to achieve termination of expiratory flow at 75% of the peak expiratory flow. Optimisation of the release time reflects the changes in elastance and therefore is personalised (i.e., conforms to individual patient pathophysiology), and adaptive (i.e., responds to changes in elastance over time).

***Summary**:* APRV using the TCAV method is a paradigm shift in protective lung ventilation which primarily aims to stabilize the lung and gradually reopen collapsed tissue to achieve lung homogeneity eliminating the main mechanistic drivers of VILI.

***Keywords**: Airway pressure release ventilation; ARDS, mechanical ventilation, VILI*.

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) develops in response to various pulmonary or extrapulmonary insults. It is characterised by disruption of the lung endothelium and epithelium with pulmonary microvascular permeability, resulting in alveolar flooding and inflammatory pulmonary oedema [1]. Consequently, the ARDS lung becomes small, unstable, and inhomogeneous. Regional volumes decrease heterogeneously following the gravitational gradient i.e., from the inflated lung mainly located in the non-dependent regions, to the gasless atelectatic or consolidated lung tissue found in the most dependent regions [2].

The primary management option currently available for ARDS is supportive mechanical ventilation (MV) to preserve life and buy time to enable the primary disease causing this syndrome to resolve [3]. During this process, however, mechanical ventilation can cause "ventilation-induced" lung injury (VILI), thereby worsening patient outcomes [4]. Airway pressure release ventilation (APRV) is a modality of ventilation in which higher inspiratory continuous positive airway pressure (CPAP) alternates with brief releases with the aim of first stabilising and then recruiting the lung. APRV can be provided as a completely mandatory mode, in spontaneously breathing patients, and during weaning and liberation from MV.

In this review, we will briefly discuss the rationale for APRV as a lung protective strategy and then provide a practical introduction to initiating APRV according to the *time-controlled adaptive ventilation (TCAV)* method. This method incorporates an extended inspiratory time ($T_{high}$) so that the inspiratory pressure ($P_{high}$) and volumes can be distributed more uniformly within the lung, and a brief expiratory time ($T_{low}$) to prevent collapse of fast emptying regions, and these settings are adjusted based on dynamic changes in lung elastance.

## CONCEPTUAL LIMITATIONS OF CURRENT LUNG PROTECTIVE STRATEGIES

The prevalent ventilatory strategy for ARDS involves delivering low tidal volumes (to avoid excessive strain of the non-dependent lung); at least moderate positive-end expiratory pressure (PEEP) to counterbalance gravitational forces and minimise atelectasis [5], with prone position to achieve both the above goals, while most importantly achieving greater lung homogeneity [3]. The only intervention that has proven to ameliorate excessive strain, gravitational forces, and atelectasis is prone positioning [6]. Other interventions, such as

recruitment manoeuvres [7, 8], higher PEEP settings [7, 9], low or even ultra-low tidal volumes (based on predicted body weight (PBW)) [10] delivered at a high rate [11, 12], have demonstrated no effect on patient outcomes in comparison with more traditional tidal volumes less than 12 mL/Kg. Some interventions have even proven to increase the risk of harm or death in patients with moderate to severe ARDS [7, 10, 11]. Therefore lung protective ventilation could be considered more of a "damage control" method of ventilation, as its primary stated aim is to limit injury, but not to reverse the main drivers of VILI (*i.e.,* loss of inflated lung, alveolar heterogeneity, and alveolar instability) [13].

It seems logical, therefore, that stabilising the lung and preventing further atelectasis may preserve lung volume, avert VILI progression, and gradually return the lungs to their previous state i.e., inflated and homogeneous. The initial catalyst of VILI may be development of micro-atelectasis [14] and formation of fluid-filled alveoli (oedema) scattered throughout the lung [15]. These changes generate a physical interface between areas with different respiratory system elastance ($E_{RS}$) [15-17]. This in turn causes a 2-4 fold concentration and amplification of local mechanical forces [15, 18-21], eventually leading to volutrauma and stress failure [21-24] perpetuating lung injury. Atelectatic areas may progress to consolidation and then fibrosis leading to prolonged mechanical ventilation [25-27].

**RATIONALE FOR APRV USING THE TCAV METHOD**

Heterogeneous oedema and loss of surfactant make the affected alveoli "sticky" [28], with alveolar opening becoming *time and pressure dependent.* This means that the lungs collapse relatively quickly (<0.5 seconds) once a threshold closing pressure is reached [29-33]. They also require a longer inspiratory time above the opening pressure to fully inflate given wide heterogeneity in the distribution of alveolar opening (and closing) time constants. To counterbalance these pathological changes, a mechanical respiratory cycle should include a sufficiently extended inspiratory time to inflate regions with a longer inspiratory time-constant. It should also comprise a sufficiently brief expiratory time (<0.5 seconds) [34] to prevent rapid collapse of lung units with a short expiratory time constant [35]. This is particularly important in severe disease with greater presence of inadequately aerated lung regions and higher elastance (i.e., fast recoil).

Although the ARDSNet recommendations follow the logic of protecting the small baby lung, the combination of a relatively short inspiratory time and longer expiratory time is incongruous with a strategy that stabilises the alveoli and over time achieves recruitment, re-inflation, and homogeneity [36]. This is particularly incongruous given that the recommended PEEP levels required to maintain tidal recruitment are 24-25 $cmH_2O$ [37]. This level of PEEP would generally lead to unacceptable plateau pressures and significant adverse cardiovascular consequences. Importantly, APRV is one of three interventions for ARDS that are not currently standard of care, despite evidence of potential effectiveness [38]**.** Recent systematic reviews suggest that APRV might reduce the time spent on mechanical ventilation and mortality [39-43]. However, evidence certainty is low because of methodological limitations and trial heterogeneity.

APRV using the TCAV method consists of a CPAP inspiratory phase periodically interrupted by releases brief enough to achieve a set reduction in end-expiratory flow compared to its peak [36, 44, 45]. The TCAV method rapidly achieves lung stability with this brief expiratory time and then progressively and gradually recruits alveoli through an *"inflate and brake ratchet-like"* mechanism while preventing expiratory collapse [46]. This concept of rachet and brake mechanism is equivalent to a system that allows motion in only one direction and prevents movement to slide back to the previous position (like a car handbrake). In this sense the ventilator during inspiration inflates and recruits the lung thanks to the $P_{high}$ and the longer inspiratory time ($T_{high}$), while the short $T_{low}$ will not allow sufficient time for derecruitment to occur, and therefore $T_{low}$ acts as a brake to deflation. The next breath will start the cycle from the previous lung volume to achieve further recruitment and stabilisation. This is different from other modes of ventilation when recruitment-derecrutiment can occur with consequent tidal inflation and deflation. A crucial aspect of the TCAV method is that it is achieved by optimising the timing of each breathing phase. A longer inspiratory time recruits more lung tissue without large transient increases in airway pressure and mechanical power, such as occurs during a conventional recruitment manoeuvre. Once lung units begin to open, alveolar interdependence drives aeration of adjacent collapsed regions [62] and the cycle of stabilisation-reaeration-homogenisation. In addition, once the opening threshold pressure is reached and the collapsed airway inflates pressure then propagates inflating more airways and alveoli.

The brief duration of the Release Phase using the TCAV method acts as a '*brake'* to prevent newly recruited tissue from re-collapsing. Furthermore, the brief Release Phase is sufficiently short so that the lung does not fully depressurize maintaining a "time-controlled" PEEP (TC-PEEP). This dual method of *time* (brief Release Phase and *pressure* (TC-PEEP) is effective for stabilizing the lung and obtaining optimal end-expiratory lung volume [29-31, 45, 47]. This method may be superior to traditionally applied PEEP [48], provided that the $T_{low}$ is appropriately set (see below) to prevent deflation [49], and is adapted according to changes in elastance as the lungs recover or deteriorate.

## HOW TO USE APRV WITH THE TIME CONTROLLED ADAPTIVE VENTILATION (TCAV) METHOD

### APRV SETTINGS

Setting APRV based on the TCAV method (Figure 1) requires an understanding that APRV is a pressure-controlled and time-cycled mode, in which spontaneous breathing can (although does not have to) occur throughout the breathing cycle (i.e., both the inspiratory and expiratory phases). APRV has essentially four settings. Two determine the ***inspiratory cycle:*** inspiratory pressure (i.e., high pressure -$P_{high}$), and inspiratory time (ie., time at high pressure - $T_{high}$) and make up the inspiratory or CPAP Phase. Two determine the ***expiratory cycle:*** expiratory pressure (i.e., $P_{low}$), and expiratory time (i.e., time at low pressure - $T_{low}$) and make up the expiratory or Release Phase (Figure 2A and Figure 2B). Once set, these settings should be reviewed periodically, minimum once very 12 hours, when clinical conditions change, or when certain events (e.g., disconnection from ventilator, transfer outside ICU, bronchoscopy or physiotherapy) occur.

#### *Setting of $P_{high}$*

The initial $P_{high}$ is generally set to match the plateau pressure achieved by the conventional mode prior to transition. For patients who receive APRV immediately following intubation, $P_{high}$ is set starting at 25 $cmH_2O$. It is then titrated upwards or downwards by 1-2 $cmH_2O$ at a time to a minimum of 20 and a maximum of 30 $cmH_2O$ to achieve minimum tidal volumes > 4-5 mL/Kg PBW. As with all settings in APRV, $P_{high}$ requires titration over time in response to changes in lung volume and compliance. This ensures optimal volumes and lung inflation pressures. For example, a flat diaphragm appearance on chest-radiograph and large release volumes can indicate excessive $P_{high}$.

***Setting of $P_{low}$***

The $P_{low}$ is the set level of external pressure applied during expiration. $P_{Low}$ does not determine the end-expiratory pressure. This is because the brief $T_{low}$ does not allow complete expiration and therefore does not equilibrate with the mouth pressure resulting in TC-PEEP. Instead, end-expiratory pressure is determined by the interaction between lung mechanics, $P_{high}$, and $T_{low}$. Therefore, $P_{Low}$ is best set at 0 $cmH_2O$ to maximize pressure gradient and expiratory flow.

***Setting of $T_{low}$***

The setting of $T_{low}$ is one of the most important and distinctive features of the TCAV method. This separates it from pressure control ventilation using an inverse ratio or other methods to set APRV [50]. In APRV using the TCAV method, $T_{low}$ is set based on lung mechanics and the patient's expiratory flow rate. The $T_{low}$ should be set to correspond to a termination expiratory flow ($T_{EF}$) (i.e., the point at which expiration is terminated) that is 75% of the initial peak expiratory flow ($P_{EF}$) (Figure 3). Lastly, lung volume may be more precisely controlled with the brief $T_{low}$ as flow and time are integrals of volume. Using time control of flow directly regulates end-expiratory lung volume (EELV) as opposed to setting a pressure (i.e., PEEP) to indirectly control EELV, avoiding volume loss from differences between the minimum and maximum closing volume[51].

We recommend first setting the $P_{high}$ as described above, then using an initial $T_{low}$ of 0.5 seconds for 1-3 breaths. Using the ventilator "freeze waveform" function, it is possible to quantify the $P_{EF}$. The $T_{low}$ can then be adjusted so that the $T_{EF}$ is 75% of the $P_{EF}$ (Figure 3). A $T_{low}$ that is too long may decrease the end-expiratory pressure leading to derecruitment and atelectrauma. A $T_{low}$ that is too brief may cause overinflation and volutrauma. As lung mechanics change, the expiratory flow characteristics change and importantly the $T_{low}$ will need titration to maintain the same expiratory flow % and therefore end-expiratory lung volume (Figure 4).

***Setting of $T_{high}$***

When transitioning to APRV, a $T_{high}$ < 4 seconds may be needed initially to maintain the respiratory rate (RR) and tidal volume (i.e., minute ventilation - VE) close to that of the

conventional ventilation mode used before transition. This is because APRV may initially drop the VE resulting in hypercapnia if the $T_{high}$ is set between 4-6 seconds and the lung has not yet recruited to sufficiently exchange $CO_2$. As the lungs recruit slowly, the $T_{high}$ can be increased. This lowers the RR but does not negatively impact $PaCO_2$ since the increased diffusion area with lung recruitment greatly accelerates gas exchange. As lung units are recruited (Figure 5), the lung efficiency ($VCO_2$/VE) improves. This will maintain $PaCO_2$ while increasing lung stability and maintaining alveolar stability-inflation-recruitment.

To select a $T_{high}$ necessary to maintain the same RR as used on conventional ventilation, calculate the current respiratory cycle time using 60/RR then subtract the set $T_{low.}$ Once the patient is fully transitioned to APRV, the $T_{high}$ is generally titrated between 4.0 and 6.0 seconds as the lung fully reopens. It is important to highlight that the setting of $T_{high}$ is one of the main determinants of mean airway pressure and minute ventilation - and therefore $CO_2$ clearance- when APRV is used as a mandatory mode. Later, when patients are able to breathe spontaneously, $T_{high}$ determines the time the patient spends breathing at higher CPAP. Therefore, while during mandatory ventilation $T_{high}$ is the inspiratory time, during spontaneous breathing the true inpiratorry time will be the patient's own neural time and $T_{high}$ will represent the time spent at CPAP.

**TRANSITION CHALLENGES**

Transitioning from a conventional ventilation mode may result in a decrease in mean arterial pressure (MAP). This may be due to unrecognized hypovolemia despite an acceptable blood pressure prior to transition. Ensuring optimal volume status and a cautious $P_{high}$ up-titration is generally sufficient to blunt the magnitude and duration of hypotension.

**Weaning APRV**

When the patient is ready for weaning based on readiness criteria[52], a "stretch test" can be performed by increasing $T_{high}$ to 30 seconds for 5-6 minutes to ascertain the presence of a satisfactory spontaneous breathing rate, rhythm, and volume. In some cases, patients with satisfactory spontaneous breathing and no signs of increased work of breathing, a fast track wean to CPAP can be used without the need for progressive extension of $T_{high}$ and reduction of $P_{high}$. In other cases, APRV weaning is achieved through a gradual increase in $T_{high}$ (0.5 - 1

sec adjustments), essentially increasing the CPAP Phase, combined with a gradual decrease in $P_{high}$. Increasing the $T_{high}$ while decreasing the $P_{high}$ results in fewer releases and more spontaneous breathing, eventually transitioning to CPAP without release. No additional assistance in the form of pressure support is generally necessary. The lengthening of the $T_{high}$ and transition to CPAP depends on the patient's response and work of breathing i.e., respiratory drive (P0.1), effort (the delta occlusion pressure – $\Delta P_{occ}$ via an expiratory occlusion manoeuvre [53], rapid shallow breath index [54], or if available oesophageal pressure swings) and presence of a regular spontaneous RR[55-57]. The acutely injured lung may remain *time*- and *pressure-dependent* for a period of hours to days, even when the chest radiograph, arterial blood gases, and lung compliance suggest otherwise. Therefore, it is important not to rely solely on these parameters when weaning APRV, but to incorporate gas exchange data into a wider clinical assessment which includes weaning criteria [52] and the response to incremental increases in inspiratory time and reduction in inspiratory pressure.

**CONCLUSIONS**

APRV using the TCAV method is a novel protective ventilation strategy that *first stabilizes and then gradually reopens* collapsed lungs. It is a personalized and adaptive approach designed to (i) rapidly stabilise alveoli immediately preventing repetitive alveolar collapse and expansion (RACE), and (ii) reinflate a small volume of collapsed tissue with each breath using an *inflate & brake ratchet-like mechanism* over hours or days. This is accomplished by adjusting the inspiratory and expiratory times, based on changes in $E_{RS}$. This method is conceptually different from the more traditional lung protective ventilation strategy.

**Key points:**

- Loss of surfactant function with acute lung injury causes regional alveolar instability (Repetitive Alveolar Collapse and Expansion - RACE) and overdistension-induced stress-multipliers which are the mechanisms of VILI at the alveolar level.
- Surfactant dysfunction causes the lungs to become *time*- and *pressure-dependent*.
- Airway Pressure Release Ventilation using the TCAV method, based on this pathophysiologic knowledge, adjusts inspiratory and expiratory time to first stabilize and then gradually reopen collapsed lung units, counteracting the main drivers of VILI.

- The TCAV method is a paradigm shift in protective lung ventilation i.e., from the current low $V_T$ to protect the 'baby lung' from overdistension approach, and the open lung approach, to a novel *Stabilize the Lung Approach*.

**Legends**

**Figure 1: Flow chart illustrating setting** airway pressure release ventilation (APRV) using the time-controlled adaptive ventilation (TCAV) method during different phases of ventilation: 1) transition from a conventional mode to APRV (*transition*), 2) *optimisation* of settings in the hours that follow application of APRV; and 3) *stabilisation* in the hours to days and finally weaning and liberation. LEGEND: $T_{high}$: inspiratory time ($T_{high}$); expiratory time ($T_{low}$); respiratory rate (RR); inspiratory pressure ($P_{high}$); expiratory pressure ($P_{low}$); tidal volume ($V_T$); plateau pressure ($P_{PLAT}$); termination of expiratory flow ($T_{EF}$); peak expiratory flow ($P_{EF}$).

**Figure 2: A)** Ventilator screen of a patient ventilated using airway pressure release ventilation (APRV) using the time-controlled adaptive ventilation (TCAV) method. The settings include high and low pressures ($P_{high}$ and $P_{low}$) at time spent a high and low ($T_{high}$ and $T_{low}$). In **panel B** the continuous positive airway pressure (CPAP) and release phases are highlighted with the respective settings of pressure and time.

**Figure 3**: Ventilator screen of a patient ventilated using airway pressure release ventilation (APRV) using the time-controlled adaptive ventilation (TCAV) method. The figure illustrates the criterion for setting $T_{low}$ expiratory flow-time waveform. The $T_{low}$ is set to achieve a termination of expiratory flow ($T_{EF}$) 75% of peak expiratory flow ($P_{EF}$). For example, if the $P_{EF}$ is 80 L/min, the $T_{low}$ should be set to achieve an end-expiratory flow ($T_{EF}$) of 60 L/min (i.e., 80 x 0.75 = 60).

**Figure 4:** The figure shows an expiratory flow wave and how changes in compliance lead to a different recoil of the respiratory system (faster in patients with worse compliance, and more acute expiratory flow). Changes in compliance require a change in the $T_{low}$ to maintain termination of expiratory flow ($T_{EF}$) 75% of peak expiratory flow ($P_{EF}$).

**Figure 5**: Electrical Impedance tomograms showing regional ventilation during conventional lung protective ventilation (A); after a short recruitment manoeuvre (B) and on airway pressure release ventilation (APRV) after 5 minutes (C), 45 minutes (D), and 90 minutes (E) from transitioning. The figure shows progressive recruitment following APRV

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