

Airway pressure release ventilation in patients with acute respiratory distress syndrome: not yet, we still need more data!

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Airway pressure release ventilation (APRV) is a pressure-limited and time-cycled mode of mechanical ventilation that is without the need for patient-ventilator interaction. The original concept, first described by Downs and Stock in 1987, was to keep the patient at an elevated continuous positive airway pressure (CPAP) pressure most of the time, with periodic releases to facilitate CO₂ clearance (1). Over the last 30 years, many studies of APRV have used a variety of different settings (*Table 1*) (7). This has caused confusion over what exactly an APRV mechanical breath profile is, and has contributed to the slow growth of evidence (7,8). Additionally, randomized controlled trials (RCTs) of APRV used control strategies that allowed tidal volumes that would not be considered lung protective by current standards (2-4). The lack of standard APRV settings, inconsistent use of lung protective ventilation in the comparator group, and the paucity of RCTs has led to appropriate skepticism about the true value (if any) of this mode.

There are four parameters (aside from FiO₂) that need to be set when using APRV; pressure high (Phigh), pressure low (Plow), time high (Thigh; set by adjusting frequency on some ventilators), and time low (Tlow) (9). More recently, setting APRV has typically used an approach of maintaining Phigh for 90% of the ventilation time and adjusting Tlow during exhalation according to the expiratory flow pattern of the patient, to maintain an open-lung approach (with

auto-PEEP) (8). Two RCTs have now used this approach as the basis for their APRV strategy, and they both used low tidal volume ventilation as their control strategy (5,6).

Since APRV is considered an open-lung approach that aims to increase mean airway pressure, minimize plateau pressure, promote lung recruitment, and improve oxygenation, it has been used and studied in patients with acute respiratory distress syndrome (ARDS). Despite this strong physiological rationale and numerous preclinical and clinical data, the study by Zhou *et al.* is the only RCT of APRV compared to low tidal volume ventilation in patients with ARDS (6). In this trial, 138 patients meeting ARDS criteria according to the Berlin Definition with a PaO₂/FiO₂ ≤250 mmHg were randomized to receive APRV or low tidal volume ventilation delivered by volume-assist control (10). They found significantly more ventilator free days (VFDs) at 28 days (19 *vs.* 2; P<0.001), and shorter ICU days (15 *vs.* 20; P=0.015) in the APRV group (6). ICU mortality was lower in the APRV group (19.7% *vs.* 34.3%; P=0.053), but this was not statistically significant. However, we feel the devil may be in the details.

There were differences between the APRV and control groups that were important, but seemed to be addressed by the authors. First, despite randomization the baseline characteristics were not evenly matched, with more patients with comorbidities randomized to the control

Table 1 Initial settings used in randomized controlled trials of APRV

Randomized controlled trial	Year	n	Phigh	Plow	Thigh	Tlow
Putensen <i>et al.</i> (2)	2001	30	Same as control	Same as PEEP in control group	Same as control	To allow expiratory flow to zero
Varpula <i>et al.</i> (3)	2003	33	Same as control	Same as PEEP in control group	Determined by frequency (12/min)	To allow expiratory flow to zero
Varpula <i>et al.</i> (4)	2004	58	Same as control	Same as PEEP in control group	4 seconds	1 second
Maxwell <i>et al.</i> (5)	2010	63	Plateau pressure from original ventilator settings	Zero	4 seconds	25–75% of PEF
Zhou <i>et al.</i> (6)	2017	138	Plateau pressure from original ventilator settings	5 cmH ₂ O	Determined by frequency and Tlow (10–14/min)	≥50%

APRV, airway pressure release ventilation; Phigh, pressure high; Plow, pressure low; Thigh, time at high pressure; Tlow, time at low pressure; PEF, peak expiratory flow.

group. Secondly, the sedation protocol allowed respiratory therapists to further titrate sedation and analgesia to achieve a minimum level of spontaneous ventilation between 30–60% of total minute ventilation in the APRV. As a result, there was significantly lower fentanyl and midazolam use in the APRV group, as well as lower sedation depth. The investigators attempted to address these concerns (i.e., imbalance in chronic diseases and sedation use) by performing a post hoc multivariable analysis in which APRV and sedation use were both independently associated with more VFDs.

For those less than enthusiastic over the current evidence for APRV the question still remains, how could APRV use result in more VFDs? One possible explanation is the limitation mentioned in the discussion by Zhou *et al.* that was not measured: patient-ventilator interaction.

Patient-ventilator interaction

One of the unique features of APRV, as already mentioned, is that it is pressure-limited and time-cycled without the need for patient-ventilator interaction. While asynchronies could exist at the moment of release, 90% of the time is spent at one elevated pressure, which by design allows minimal time for patient-ventilator asynchrony to occur. For the control group, Zhou *et al.* study used volume-assist control with inspiratory flow rates set close to 40 L/min and a decelerating flow pattern (as seen in the images provided in the electronic supplemental materials; ESM2). On the Puritan Bennet 840 ventilator (Covidien, Medtronic Inc. Minneapolis, MN) the set flow rate in volume-assist

control is the maximum flow, that gradually slows down during inspiration when using a decelerating flow pattern. The results in longer inspiratory times compared to using constant flow. Longer inspiratory times can lead to delayed cycling, which can cause increased muscle workload, and ineffective efforts (11). Patients were switched to pressure support only to perform a spontaneous breathing trial (SBT), and if they failed, they were returned to the previous volume-assist control settings. When looking at the supplemental data (ESM2) there are two interesting findings. First, there are two ventilator screen images of a patient being managed with volume-assist control. The flow-time waveforms clearly show nearly half of the patient efforts are ineffective (*Figure 1A,B*). Secondly, the protocol (ESM1) dictates 6 mL/kg of predicted body weight (PBW) to be used, with the ability to increase tidal volume to 7 or 8 mL/kg if sufficient dyssynchrony is noted and plateau pressure is less than 30 cmH₂O. By day three of the study, the mean (\pm standard deviation) of the set tidal volume was 7 \pm 1 mL/kg PBW (ESM2).

Asynchrony is associated with longer duration of mechanical ventilation, longer ICU stay, and increased ICU and hospital mortality (12–14). The final statement in the discussion by Zhou *et al.* mentions that patient-ventilator interaction was not measured, and that whether it could affect the outcomes would require further study.

Other considerations

In recent years, some sobering data has been published related to an open-lung approach. The Oscillation in

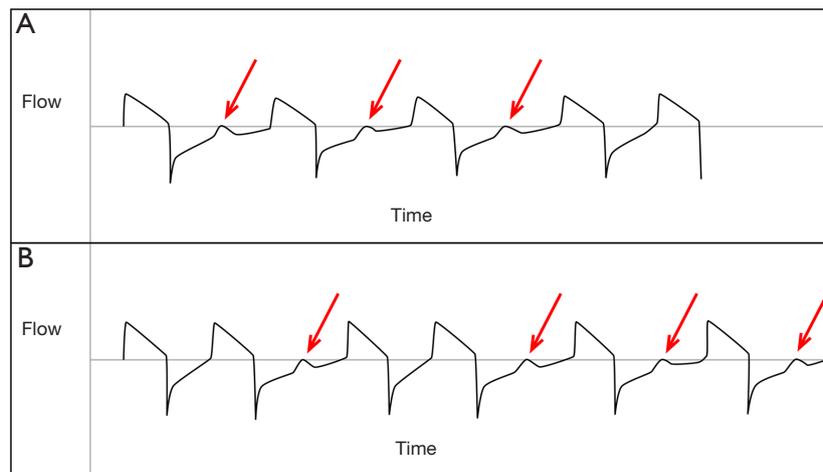


Figure 1 Graphical representation of the flow-time curves of two images included as Figure SS2 in the electronic supplemental material (ESM2) of the Zhou *et al.* study. Red arrows represent ineffective efforts by the patient. (A) Shows 5 triggered breaths and 3 ineffective efforts; (B) shows 6 triggered breaths and 4 ineffective efforts.

Acute Respiratory Distress Syndrome (OSCAR) and Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trials of high-frequency oscillatory ventilation (HFOV) found no benefit, and even harm, when HFOV was used early to manage patients with ARDS (15,16). Additionally, the recent Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) trial compared low-tidal volume and low-moderate PEEP to lung recruitment and PEEP set according to best respiratory system compliance (17). The study found significantly higher mortality using the open-lung approach of lung recruitment and compliance-based PEEP, and the VFDs were 0 in both groups. APRV is an open-lung approach that has not been tested to the extent that these other methods have, and particularly in light of these results, the potential efficacy of APRV requires confirmation in a large, rigorously conducted RCT.

Conclusions

We now have one small RCT of ARDS patients that compared APRV to low tidal volume ventilation. Although the study demonstrated improvements in a number of patient outcomes, there were a number of important limitations, including a control group that had a greater potential for patient-ventilator asynchrony that may have resulted in fewer VFDs and longer duration of ICU and hospital stay. Additionally, despite the fact that an open-lung approach has a strong physiological basis for its use

based on animal data and small clinical trials, we have yet to see a large RCT demonstrate improvements in patient outcomes. Until then, we have ongoing equipoise regarding APRV, and do not recommend its routine use in patients with ARDS.

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Footnote

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