Caution—Do Not Attempt This at Home. Airway Pressure Release Ventilation Should Not Routinely Be Used in Patients With or at Risk of Acute Respiratory Distress Syndrome Outside of a Clinical Trial

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In this opinion piece, we review reasons why airway pressure release ventilation (APRV) should not routinely be used in clinical practice in patients with or at high risk of acute respiratory distress syndrome (ARDS) because it has not been demonstrated to be effective nor safe based on clinical trial evidence.

Several strategies to best oxygenate and ventilate mechanically ventilated patients have been tested over the past 30 years, with some demonstrating efficacy and some not (1). In patients with established ARDS, the best evidence demonstrates that lung-protective ventilation using low tidal volume ventilation reduces mortality when compared with the use of high tidal volume and high-pressure ventilation (2). In contrast, approaches using high positive end-expiratory pressure (PEEP) versus low PEEP, open lung ventilation with recruitment maneuvers, esophageal balloon titrated end-inspiratory and end-expiratory transpulmonary pressures, as well as high-frequency oscillation have all failed to improve patient survival compared with standard lung-protective ventilation (3–8).

APRV is an alternative mode of ventilation that uses an open lung ventilation strategy (9). APRV has two conceptual advantages: 1) to maintain a mean airway pressure that is higher than the closing pressure of alveoli and 2) to allow a patient unrestricted spontaneous breathing throughout the respiratory cycle (10). It is characterized by bilevel pressure control (high pressure [P_{high}] and low pressure [P_{low}]) that time cycles with a prolonged inverse ratio. The time spent at P_{high} (T_{high}) facilitates alveolar recruitment, whereas a short time at P_{low} (T_{low}) allows for ventilation and carbon dioxide (Co_2) clearance without risking alveolar derecruitment. If patients are heavily sedated or pharmacologically paralyzed and there is an absence of spontaneous breathing, then APRV becomes very similar to inverse ratio pressure control ventilation. As pressure is cycled between P_{high} and P_{low}, the tidal volume delivered will depend upon the compliance and resistance of the respiratory system. For example, patients with low compliance due to ARDS will receive low tidal volumes for a given P_{high}/P_{low} combination.

There is biologic plausibility as to why APRV use to maintain spontaneous ventilation and an open lung may be beneficial, particularly in ARDS. Animal studies have demonstrated that spontaneous ventilation during APRV can

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lead to an improvement in atelectasis and ventilation-perfusion matching, especially in the posterior/dependent parts of the lung closest to the diaphragm (11, 12). Experimental studies in swine, rat, canine, and rabbit models have also demonstrated improved oxygenation (13). Allowing spontaneous ventilation may also reduce the need for sedation and paralytics and their corresponding adverse effects. Conversely, it is also plausible that a physiologic basis for harm exists through multiple mechanisms including a reduction in cardiac preload from increased intrathoracic pressure, lack of breath-to-breath assistance during spontaneous ventilation leading to desynchrony, ventilator-induced lung injury from unregulated high tidal volumes or pressures, and acidosis from inadequate clearance of Co_2 during the pressure release phase (9).

Despite these potential benefits, the fate of APRV in clinical trials thus far is similar to that of other open lung ventilation approaches (4, 5, 7, 8) and fails to convincingly demonstrate that any of the benefits of APRV improve patient outcomes. Randomized control trials (RCTs) examining the use of APRV are summarized in **Table 1**. In total, eight APRV RCTs enrolled 548 patients (285 randomized to APRV and 263 randomized to standard management) (14–21). These studies are heterogenous in both the patient populations studied and the APRV variables applied. The studies have been small (average study size of 69 patients) and associated with several challenges including protocol adherence and stopping early as well as sources of bias in interpretation (summarized in **Table 2**) (15, 19, 20). We briefly summarize the key issues and clinical trial evidence in the following paragraphs.

THE IDEAL PATIENT POPULATION FOR APRV USE REMAINS UNDETERMINED

There are three patient populations or times during a patient's course where APRV may be beneficial: 1) patients ventilated without ARDS but at risk for it; 2) patients with established and active ARDS; and 3) patients recovering from ARDS. These are important distinctions as spontaneous ventilation and larger more liberal tidal volumes may be acceptable in the first and third groups; however, the efficacy or safety of spontaneous ventilation in the second group is unproven. Randomized trials to date have focused on patients with established lung injury/ARDS (four studies, n = 338) (14, 15, 19, 20) or those without ARDS but at risk for it (four studies, n = 210) (16–18, 21). The patient populations have included hypoxemic respiratory failure (one study, n = 90) (19), lung injury/ARDS (two studies, n = 196) (14, 15), trauma patients (two studies, n = 93) (16, 17), and COVID-19 pneumonia (one study, n = 90) (19). No randomized trials have explicitly examined patients recovering (e.g., weaning) from ARDS. **Figure 1** presents a forest plot with the relative risk reductions in mortality for each study. As seen qualitatively, there is a range of effect, primarily centering on no effect but with CIs from most studies spanning from benefit to significant harm. This variability may relate to heterogeneity of patient populations or variability in APRV protocol used. Moreover, these studies may be underpowered to demonstrate any benefit or harm. Of note, three of eight studies were stopped early (Table 2 for reasons for stopping early) (15, 19, 20), and another four had no formal sample size calculation (Table 2) (16–18). For patients without ARDS, APRV's role remains unclear as no study targeted prevention of ARDS as a primary endpoint.

IDEAL SETTINGS FOR APRV REMAIN UNCLEAR

Part of the challenge with using APRV is that given the lack of proven benefit, the optimal settings or physiologic or ventilatory goals to target with APRV have not been established (13). This is illustrated by the variability in APRV protocols that have been tested (Table 1). For example, variations in how T_{low} is set can

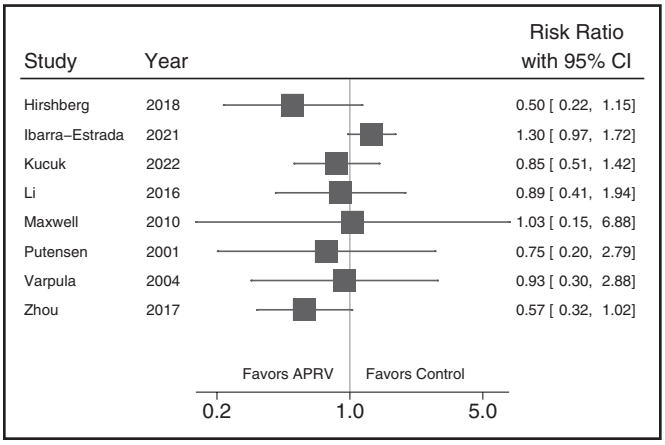

Figure 1. Forest plot of relative risks of mortality in randomized studies examining airway pressure release ventilation (APRV). Hirshberg et al (20) is comparing traditional APRV arm with the conventional volume control–low tidal volume ventilation arm.

TABLE 1.

Study Characteristics of Randomized Controlled Trials Testing the Use of Airway Pressure Release Ventilation in Patients With or at Risk for Acute Respiratory Distress Syndrome

References	Study Type	*n*	Inclusion Criteria	APRV Intervention	Control Group	Outcomes	Adverse Events
Hirshberg et al (20)	RCT Four ICUs	52	Acute hypoxemic respiratory failure	APRV traditional arm: P_{HIGH}: 3cm H_2O above mean airway pressure prior to randomization. P_{Low}: set to 0 cm H_2O. T_{HIGH}: 4–6 s based on respiratory rate. T_{LOW}: 0.4–1.0 s (stop at 50–75% of peak expiratory flow rate). $P_{0.1}$ to monitor drive to breath.	Low tidal volume 6 mL/kg PBW as per ARDSNET	**Primary:** PF ratio day 3: APRV 165 (134–209) vs APRV-LTV 165 (115–236) vs control 161 (142–184) ($p = 0.92$) **Secondary:** Hospital mortality: APRV 5/17 (29) vs APRV-LTV 6/18 (33) vs control 10/17 (59) ($p = 0.20$)	**Sedation:** APRV 53 (26–79) vs APRV-LTV 70 (42–88) vs control 64% (38–84); $p = 0.71$ **Barotrauma:** APRV 0 (0%) vs APRV-LTV 0 (0%) vs control 1 (6%); $p = 1.00$
Ibarra-Estrada et al (19)	RCT One ICU	90	COVID-19 patients within 48 hr of intubation	P_{HIGH}: plateau pressure on continuous mandatory ventilation (maximum 30 cm H_2O). P_{LOW}: 0 cm H_2O. T_{HIGH}: 4–6 s. T_{LOW}: 0.4–0.6 s (terminate at 50–75% of peak expiratory flow rate).	Low tidal volume 6 mL/kg PBW as per ARDSNET	**Primary:** 28-d ventilator-free days: APRV 3.7 vs control 5.2 ($p = 0.28$) **Secondary:** 28-d mortality: APRV 35/45 (78%) vs control 27/45 (60%) ($p = 0.07$)	**Severe hypercapnea:** APRV 19 (42%) vs Control 7 (15%); $p = 0.009$ **Barotrauma:** APRV 4 (9%) vs control 4 (9%); $p = 1.00$
Kucuk et al (21)	RCT One ICU	65	Mechanically ventilated patients with Lung Injury Prevention Score > 7	P_{HIGH}: plateau pressure or mean airway pressure on controlled mode. P_{LOW}: 0 cm H_2O. T_{HIGH}: 4 s. T_{LOW}: 0.8 s (titrate to P_{CO_2} and expiratory flow curve).	Pressure control low tidal volume 6–8 mL/kg PEEP set to 5–10 cm H_2O based on F_{IO_2}	**Primary:** Lung Injury Prevention Score (only reported among survivors) APRV 8.5 (7–12) vs control 9 (7–13); $p = 0.226$ **Secondary** Mortality: APRV 14/32 (44%) vs control 17/33 (52%) ($p = 0.705$)	**Barotrauma:** Reported as none occurred in discussion but not reported formally in both groups in results section
Li et al (18)	RCT One ICU	52	Mechanically ventilated patients	P_{HIGH}: 30 cm H_2O. P_{Low}: 0 cm H_2O. T_{HIGH}: 4–8 s. T_{LOW}: 0.4–0.8 s.	Low tidal volume 6–8 mL/kg PEEP: pressure-volume curve (pressure corresponding to lower inflection point + 2 cm)	**Mortality:** APRV 8/26 (28.5%) vs 9/26 (34.6%) control ($p > 0.05$) **28 d off ventilator time:** APRV 19.6 ± 8.2 vs control 15.1 ± 8.9	None reported

(*Contiunued*)

TABLE 1. (*Continued*).

Study Characteristics of Randomized Controlled Trials Testing the Use of Airway Pressure Release Ventilation in Patients With or at Risk for Acute Respiratory Distress Syndrome

References	Study Type	*n*	Inclusion Criteria	APRV Intervention	Control Group	Outcomes	Adverse Events
Maxwell et al (17)	RCT Two ICUs	63	Trauma patients requiring mechanical ventilation for ≥ 72 hr	P_{HIGH}: set to plateau pressure. P_{Low}: 0 cm H_2O. T_{HIGH}: variably set to spontaneous respiratory rate. T_{LOW}: (terminate at 25–75% of peak expiratory flow rate).	SIMV with pressure support with 6 mL/kg PBW	**Primary: Not formally defined** **Secondary:** Mortality: APRV 2/31 (6%) vs control 2/32 (6%) Ventilated days: APRV 10.49 d ± 7.23 d vs control 8.00 d ± 4.01 d	**Barotrauma**: APRV 0 (0%) vs control 1 (3%)
Putensen et al (16)	RCT One ICU	30	Severe multitrauma patients	P_{HIGH}: value below UIP on pressure-volume curve that provided ≤ 7 mL/kg. P_{Low}: 2 cm H_2O above LIP on pressure-volume curve. T_{HIGH}: titrated to allow flow to decelerate to zero. T_{LOW}: titrated to allow flow to decelerate to zero.	Pressure control ventilation for 72 hr followed by APRV weaning	**Primary: Cardiorespiratory function but not defined** Secondary: Mortality: APRV 3/15 (20%) vs control 4/15 (26%) (p = not significant)	Not reported
Varpula et al (15)	RCT One ICU	58	Acute lung injury patients with PF ratio ≤ 200	P_{HIGH}: driving pressure to allow 8–10 mL/kg tidal volume up to upper inflection point or < 35 cm H_2O. P_{Low}: titrated to the pressure-volume curve. T_{HIGH}: 4 s. T_{LOW}: 1 s.	SIMV with pressure support targeting 8–10 mL/kg PBW	**Primary:** 28-d ventilator free days: APRV 13.4 (±1.7) vs control 12.2 (±1.5) ($p = 0.83$) **Secondary:** Mortality at day 28: APRV 5/30 (17%) vs 5/28 (18%) ($p = 0.91$)	Not reported
Zhou et al (14)	RCT One ICU	138	Berlin acute respiratory distress syndrome with PF ratio ≤ 250	P_{HIGH}: plateau pressure on (maximum 30 cm H_2O). P_{Low}: 5 cm H_2O. T_{HIGH}: based on release frequency 10–14. T_{LOW}: 1–1.5X expiratory time constant (stop at 50% peak expiratory flow rate)	Volume-controlled ventilation targeting 6 mL/kg PBW	**Primary:** 28-d ventilator-free days: APRV 19 (8–22) vs control 2 (0–15) ($p < 0.001$) **Secondary:** Hospital mortality: APRV 17/71 (24%) vs 25/67 (37%) ($p = 0.088$)	Pneumothorax rate to day 28 APRV: 3 (4.2%) low tidal volume: 7 (10.4%); $p = 0.199$

APRV = airway pressure release ventilation, ARDSNET = acute respiratory distress syndrome network, LTV = low tidal volume, $P_{0.1}$ = occlusion pressure, PF = Pao_2/Fio_2 ratio, PBW = predicted body weight, PEEP = positive end-expiratory pressure, P_{HIGH} = high pressure, P_{LOW} = low pressure, RCT = randomized control trial, SIMV = synchronized intermittent mandatory ventilation, T_{HIGH} = time at high pressure, T_{LOW} = time at low pressure.

TABLE 2.

Potential Sources of Bias When Interpreting Randomized Trials Examining Airway Pressure Release Ventilation

References	Study Type	N	Stopping Status	Sample Size and Primary Outcome	Other potential Sources of Bias in Interpretation of Study Results
Hirshberg et al (20)	RCT Four ICUs	52	**Stopped early–**inability to consistently maintain safe tidal volumes and low enrollment	No concerns	Days on study (median) was much shorter in the APRV arms (3 d) than in the control arm (7 d)
Ibarra-Estrada et al (19)	RCT One ICU	90	**Stopped early–**data safety monitoring board review due to four episodes of barotrauma. Also inability to consistently maintain safe tidal volumes and low enrollment	No concerns	No major
Kucuk et al (21)	RCT One ICU	65	Stopping criteria not formally defined	Primary outcome ambiguous. Sample size estimation not based on primary outcome reported	Intention to treat analysis not reported. Brain dead patients ($n = 5$) listed as lost to follow-up and not analyzed
Li et al (18)	RCT One ICU	52	Stopping criteria not formally defined	Primary outcome not formally defined Sample size justification not reported	Trial protocol and analysis plan not registered or published a priori
Maxwell et al (17)	RCT Two ICUs	63	Stopping criteria not formally defined	Primary outcome not formally defined. Sample size justification not reported	Analysis excluded non-adherence protocol violations and not analyzed as intention to treat (3 patients excluded). Trial protocol and analysis plan not registered or published a priori
Putensen et al (16)	RCT One ICU	30	Stopping criteria not formally defined	Primary outcome not formally defined. Sample size justification not reported	Trial protocol and analysis plan not registered or published a priori
Varpula et al (15)	RCT One ICU	58	**Stopped early–**futility at interim analysis when approximately 2/3 of patients enrolled	No concerns	No major
Zhou et al (14)	RCT One ICU	138	No concerns	No concerns	Baseline variables for chronic conditions not balanced between APRV (lower) and control (higher). May be indicative of residual unmeasured confounding. Imbalance in number of patients assigned to APRV and control despite 1:1 randomization.

APRV = airway pressure release ventilation, RCT = randomized control trial.

range from a fixed period (15, 16, 18) to a flow-based dynamic setting (14, 17, 19–21). The principles of pressure and volume limited lung-protective ventilation are much more difficult to apply to APRV. The complexity of this issue is increased by the ability of patients to spontaneously breath throughout the respiratory cycle, along with changes in the compliance of the patient's lungs over the course of the ICU stay. Attempts to use a physiologically informed approach to APRV settings have been proposed; however, these have only been tested in nonrandomized studies (22). Other aspects of APRV settings that remain unclear include how often time cycling should occur, should patients undergo a period of stabilization prior to initiating APRV, how should titration of P_{high} be conducted, and should the size of tidal volumes and P_{high} be restricted to traditional lung-protective ranges. This uncertainty may have played a role in adhering to study protocols as one study stopped early due to challenging protocol adherence (20). Finally, although the rationale of APRV is to improve recruitment and oxygenation and permit spontaneous breathing, are these goals truly linked with better outcomes? This remains to be determined. Other randomized trials examining mechanical ventilation interventions that can improve oxygenation (such as open lung ventilation, oscillation, high PEEP) have not been associated with improved patient outcomes (3–8).

ADVERSE EFFECTS OF APRV REMAIN UNDEFINED

There are several potential pitfalls of APRV use. One major driver for adverse outcomes with APRV may be the assumption that spontaneous ventilation is always safe and appropriate, particularly for patients with ARDS or severe acute hypoxemic respiratory failure. Inappropriate spontaneous breathing can lead to excessive respiratory effort and a unique form of ventilator-induced lung injury known as patient self-inflicted lung injury (P-SILI) which has been associated with worse outcomes (23). Methods to measure respiratory drive ($P_{0.1}$) and magnitude of lung stress (pressure swing with occluded airway: P_{occ}) exist but were not part of most study protocols (24). Only one study examined $P_{0.1}$ as a marker of patient respiratory drive (20). The risk of P-SILI is real as evidenced by the APRV trial by Ibarra-Estrada et al (19) that had significant rates of barotrauma and hypercarbic respiratory failure in APRV-treated individuals and resulting in the study being stopped early. Four of the eight randomized trials on APRV (Tables 1 and 2) did not report adverse events. Barotrauma may occur independently of P-SILI and instead be related to elevated mean airway pressures. Other potential adverse effects of APRV that will need to be rigorously examined include rates of increasing vasopressor requirement due to reduced preload, rates of barotrauma due to higher mean airway pressures, and acidosis related to hypercarbia from inadequate ventilation during airway pressure release. Not only will future studies need to consider including diagnostic measures such as $P_{0.1}$ or P_{occ} to ensure patient effort is safe to initiate or maintain APRV, but a standardized list of adverse events will need monitoring to determine any association between APRV and patient harm, particularly related to P-SILI.

Although it is possible that the use of APRV may be justified in the future, current evidence demonstrates too many gaps and questions around its safe and appropriate use. Congruent with this, clinical guidelines for ARDS to date have not supported the routine use of APRV (25). Given this equipoise, APRV should only be used by exception where the risks are carefully weighed with the potential benefits. Rather than view the lack of evidence and gaps in literature as criticisms, it would be prudent to view them as opportunity for study. Given the equipoise, APRV warrants a large multicenter clinical trial that compares APRV protocols with the standard of care. At least two distinct populations will need to be studied including patients with ARDS and those recovering from it. There will be several challenges, the least of which is standardizing how APRV is set and titrated. Established therapies in the management of ARDS such as low tidal volume ventilation and prone positioning required significant study before they were ready for prime time. Many promising therapies for ARDS failed to demonstrate efficacy once studied properly (4, 5, 7, 8). Likewise, APRV still requires much work before becoming an established method of mechanical ventilation in patients with or at risk for ARDS. Until this time, to paraphrase a common aphorism, "for expert use: don't try this at home."

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