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Randomized Feasibility Trial of a Low Tidal Volume-Airway Pressure Release Ventilation Protocol Compared With Traditional Airway Pressure Release Ventilation and Volume Control Ventilation Protocols

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Objectives: Low tidal volume (= tidal volume ≤ 6 mL/kg, predicted body weight) ventilation using volume control benefits patients with acute respiratory distress syndrome. Airway pressure release ventilation is an alternative to low tidal volume-volume control ventilation, but the release breaths generated are variable and can exceed tidal volume breaths of low tidal volume-volume control. We evaluate the application of a low tidal volume-compatible airway pressure release ventilation protocol that manages release volumes on both clinical and feasibility endpoints.

Design: We designed a prospective randomized trial in patients with acute hypoxemic respiratory failure. We randomized patients to low tidal volume-volume control, low tidal volume-airway pressure release ventilation, and traditional airway pressure release ventilation with a planned enrollment of 246 patients. The study was stopped early because of low enrollment and inability to consistently achieve tidal volumes less than 6.5 mL/kg in the low tidal volume-airway pressure release ventilation arm. Although the primary clinical study endpoint was Pao_2/Fio_2 on study day 3, we highlight the feasibility outcomes related to tidal volumes in both arms.

Setting: Four Intermountain Healthcare tertiary ICUs.

Patients: Adult ICU patients with hypoxemic respiratory failure anticipated to require prolonged mechanical ventilation.

Interventions: Low tidal volume-volume control, airway pressure release ventilation, and low tidal volume-airway pressure release ventilation.

Measurements and Main Results: We observed wide variability and higher tidal (release for airway pressure release ventilation) volumes in both airway pressure release ventilation (8.6 mL/kg; 95% CI, 7.8–9.6) and low tidal volume-airway pressure release ventilation (8.0; 95% CI, 7.3–8.9) than volume control (6.8; 95% CI, 6.2–7.5; $p = 0.005$) with no difference between airway pressure release ventilation and low tidal volume-airway pressure release ventilation ($p = 0.58$). Recognizing the limitations of small sample size, we observed no difference in 52 patients in day 3 Pao_2/ Fio_2 ($p = 0.92$). We also observed no significant difference between arms in sedation, vasoactive medications, or occurrence of pneumothorax.

Conclusions: Airway pressure release ventilation resulted in release volumes often exceeding 12 mL/kg despite a protocol

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designed to target low tidal volume ventilation. Current airway pressure release ventilation protocols are unable to achieve consistent and reproducible delivery of low tidal volume ventilation goals. A large-scale efficacy trial of low tidal volume-airway pressure release ventilation is not feasible at this time in the absence of an explicit, generalizable, and reproducible low tidal volume-airway pressure release ventilation protocol. (*Crit Care Med* 2018; 46:1943–1952)

Key Words: acute respiratory distress syndrome; airway pressure release ventilation; mechanical ventilation; protocol; respiratory failure; volume control

Mechanical ventilation is a life-saving therapy in patients with acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) although it may induce ventilator-induced lung injury (VILI) (1–7). The highest quality of evidence demonstrates that a volume control (VC) ventilation strategy using low tidal volume (LTV) of 6 mL/kg of predicted body weight (PBW) with plateau pressure (P_{plat}) less than 30 cm H_2O reduces mortality in patients with ARDS compared with a target tidal volume (V_T) equal to 12 mL/kg PBW and P_{plat} less than 50 cm H_2O (1). V_Ts even 1 or 2 mL/kg above LTV in patients with ARDS are associated with increased mortality (8). Many clinicians advocate for LTV ventilation for treatment of ARDS, with some arguing benefit in patients without ARDS (9–12).

Airway pressure release ventilation (APRV) is a pressure-limited mode of mechanical ventilation observed to improve oxygenation (13–17).

APRV is proposed as an alternative to VC-LTV because it attempts to minimize time spent at a low positive end-expiratory pressure (PEEP, or P_{low}) and increase mean airway pressure (P_{aw}) by maximizing time spent at a high PEEP, or P_{high}, but it does not target release volumes (14, 18, 19). Early studies of APRV demonstrate improvements in patient's oxygenation with lower peak inspiratory pressures (PIPs) and higher P_{aw}s compared to patients treated with conventional ventilation (20–23). Observational studies also suggest an improved hemodynamic profile and enhanced patient comfort (both related to spontaneous breathing) resulting in reduced sedation requirements with APRV (24–27). PEEP optimization may improve oxygenation but occurs at the expense of higher measured tidal or release volumes that could increase VILI (28, 29). Therefore, we created an exportable APRV-LTV protocol that adapted the Habashi (14) protocol to employ an LTV ventilation strategy that targets average release volumes less than 6.5 mL/kg.

We proposed APRV-LTV would confer the benefits of APRV and limit the risk of VILI (14, 18). An ideal APRV-LTV protocol is reproducible and generalizable, enhances patient comfort, and confers advantages to hemodynamics and clinically relevant endpoints. We defined feasibility as successful implementation of an APRV-LTV protocol that consistently achieved V_T less than or equal to 6.5 mL/kg with high clinician compliance. Before conducting a large multicenter efficacy trial comparing mortality between APRV-LTV and VC-LTV, we assessed the feasibility of an APRV-LTV protocol compared with traditional APRV and VC in a randomized, three-arm design among patients with acute hypoxemic respiratory failure.

METHODS

We performed a randomized controlled feasibility trial of VC-LTV versus APRV-LTV versus APRV in patients with respiratory failure admitted to one of four ICUs located in three Intermountain Healthcare hospitals over 49 months with first enrollment in September 2011 after trial registration with clinical.trials.gov (NCT01339533). The Central Region Intermountain Institutional Review Board (IRB) approved the protocol (IRB number: 1015758) with oversight from an independent data safety and monitoring board (DSMB). We employed three explicit mechanical ventilation paper protocols in patients with respiratory failure less than 24 hours and anticipated to require the ventilator for greater than 24 hours. Patients were assigned via computer-generated permuted 3–6 block randomization with sealed, opaque, and sequentially numbered envelopes into one of three arms: 1) conventional VC-LTV ventilation, 2) APRV-LTV, and 3) traditional APRV (14) (**Supplement A**, Supplemental Digital Content 1, http://links.lww.com/CCM/E39; **Supplement B**, Supplemental Digital Content 2, http://links.lww.com/CCM/E40; and **Supplement C**, Supplemental Digital Content 3, http://links.lww.com/CCM/E41). An identical continuous positive airway pressure protocol with a trigger F_{IO_2} less than or equal to 0.60 and a PEEP or P_{high} less than or equal to 10 comprised the weaning phase, which is found in Supplement B, along with daily compliance (**Supplement D**, Supplemental Digital Content 4, http://links.lww.com/CCM/E42) and power analysis (**Supplement E**, Supplemental Digital Content 5, http://links.lww.com/CCM/E43) for planned enrollment of the initial study aimed to justify a larger multicenter efficacy trial. The study was terminated early to maximize enrollment in Prevention and Early Treatment of Acute Lung Injury Network competing trials and after a planned 50 patient data review by the DSMB revealed significant variability in V_Ts in the APRV-LTV protocol.

Protocols

We operationalized the three protocols with decision tree logic for adhering to each arm's stated purpose (Supplement A, Supplemental Digital Content 1, http://links.lww.com/CCM/E39; Supplement B, Supplemental Digital Content 2, http://links.lww.com/CCM/E40; and Supplement C, Supplemental Digital Content 3, http://links.lww.com/CCM/E41). We used the Draeger EvitaXL ventilator (Draeger, Houston, TX) for all protocols. Each protocol was written in paper format with cell branching logic as a preliminary step for computerization and exportability. The VC-LTV titrates PEEP and F_{IO_2} based on the ARDS Network (ARDSNet) recommended F_{IO_2} and PEEP tables modified for high altitude (1, 30). The oxygenation and ventilation tables were used by our institution in ARDSNet trials. The VC-LTV protocol sets a target V_T of 6.0 mL/kg but

with auto-flow can result in measured V_T greater than 6.0 mL/kg. Release volumes and V_Ts are measured as exhale volumes at the exhalation valve of the ventilator. Respiratory therapists interact with the patient and the ventilator at least every 2 hours, often more frequently, and record the average values over several breaths in the electronic ventilator record. APRV-LTV titrates P_{low} and/or P_{high} to target release volumes equal to 6.0 mL/kg. Traditional APRV followed previously published protocols (14) (Supplement C, Supplemental Digital Content 3, http://links.lww.com/CCM/E41). APRV-LTV was developed by two respiratory therapists and three pulmonary and critical care physicians and involved testing in an artificial lung simulation laboratory with quality improvement project iterative refinement of the protocol during clinical care (Supplement B, Supplemental Digital Content 2, http://links.lww.com/CCM/E40). All participating clinicians stated equipoise regarding the study.

After randomization, the respiratory therapist set the ventilator parameters per the specific arm protocol directions. APRV settings were determined by setting P_{high} 3 above the P_{aw} reading for the patient before randomization. Traditional APRV settings followed the Habashi (14) protocol to set P_{low} equal to 0 with time$_{high}$ and P_{low} titrated per patient response. APRV-LTV settings were determined by setting P_{high} 3 above the P_{aw} reading for the patient before randomization. P_{low} was set at a minimum of 5 and titrated with P_{high} to target a release volume equals to 6 mL/kg. Work of breathing for each patient was observed and adjusted for P.01 as described in the protocol (Supplement B, Supplemental Digital Content 2, http://links.lww.com/CCM/E40; and Supplement C, Supplemental Digital Content 3, http://links.lww.com/CCM/E41).

Data Collection

As part of standard clinical practice, respiratory therapists measure and electronically record ventilator parameters every 2 hours, including P_{aw}, PIP, V_T, exhaled volume, and P_{plat} when indicated. We report average daily ventilator parameters. V_T (mL/kg PBW) was defined as the measured exhaled volume for the VC-LTV and the measured exhaled release volume each APRV arm. We also collected the exhaled volume and rate of spontaneous breaths in the APRV arms. P_{high} and PIP were treated as interchangeable for APRV, and P_{plat} is not measured. Lowest mean arterial pressure (MAP) and average daily central venous pressure (CVP) were also recorded. The medication dosing data were reported for baseline day as randomization time to 6:00 AM the following day, and then 6:00 AM to 6:00 AM for each subsequent study day. Dosage is summarized only for days when medications were administered. Total dosing for vasoactive medications was calculated as the sum of the norepinephrine equivalent (NEE) doses for each vasoactive medication (31).

Subjects

We screened all patients greater than or equal to 18 years old with hypoxemic respiratory failure daily (**Fig. 1**). Informed consent was obtained by qualified surrogate. Randomization blocks were stratified as either ARDS or hypoxemic respiratory failure. If patients met the criteria for ARDS (Pao_2/Fio_2 ratio, chest radiograph infiltrates, absence of clinical evidence of left atrial hypertension) (1), they were stratified to the ARDS

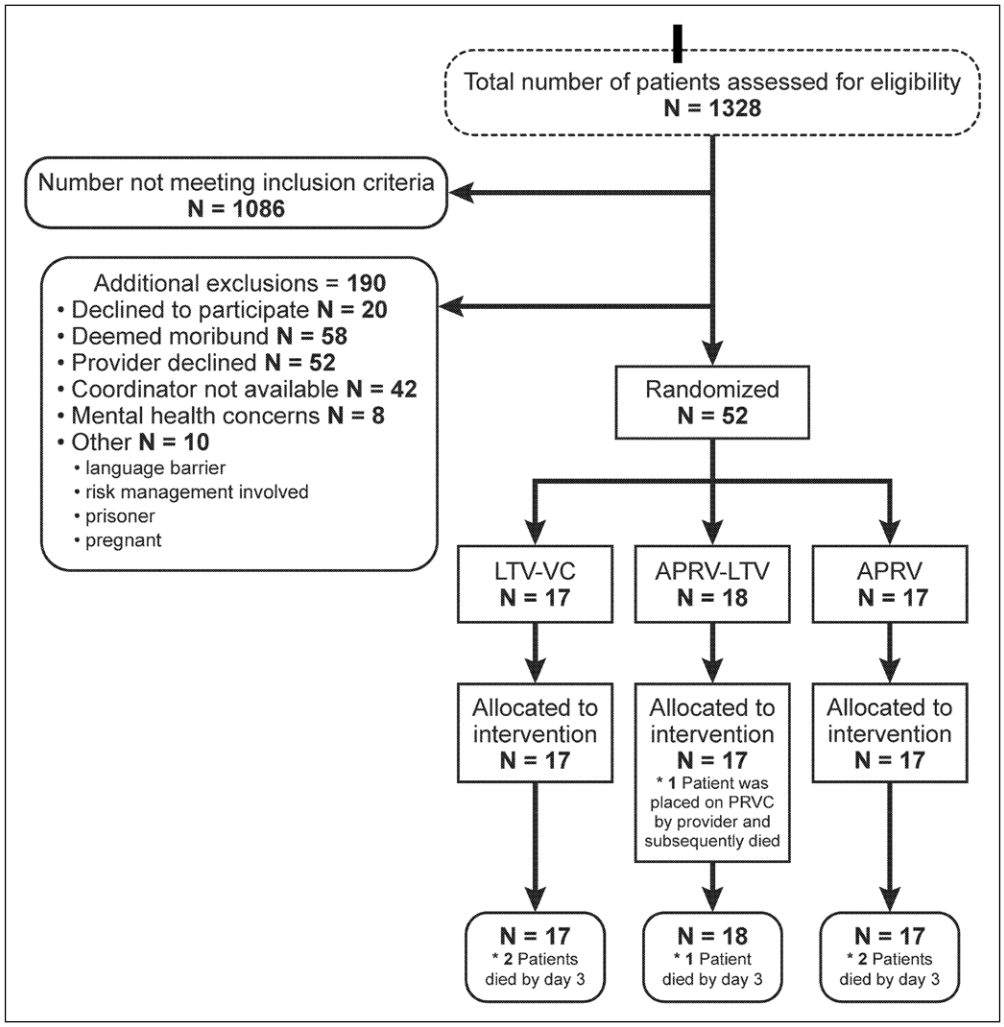

Figure 1. Consort diagram. *Primary analysis was Pao_2/Fio_2 ratio on study day 3. APRV = airway pressure release ventilation, LTV = low tidal volume, PRVC = pressure-regulated volume control, VC = volume control.

group. Otherwise patients were stratified as hypoxemic respiratory failure. Patients were randomized within 24 hours of the initiation of invasive mechanical ventilatory support.

We excluded patients with known pregnancy or a primary diagnosis of acute coronary syndrome, major cardiac dysrhythmia, severe chronic respiratory disease, or severe traumatic head injury. We also excluded patients receiving chronic mechanical ventilation, neuromuscular disease, moribund patients, or patients enrolled in another interventional trial.

Statistical Analysis

The primary outcome was Pao_2/Fio_2 at day 3. Secondary outcomes included hospital mortality, ICU and hospital length of stay (LOS), ventilator-free days (VFDs), sedation medication received, vasoactive medication received, reintubation, and barotrauma. We used the Kruskal-Wallis test for three-way comparison of the continuous outcomes and Fisher exact test for the binary outcomes. We also performed a linear regression analysis adjusted for severity of illness (using Acute Physiology and Chronic Health Evaluation II) for clinical outcomes. We compared daily administration of vasoactive medications, sedatives, benzodiazepines, opioids, atypical antipsychotics, and paralytics for each protocol. We also compared total daily dosages of continuous medications including weighted mean NEE, dexmedetomidine, and propofol. As we collected the ventilator parameters, medication information, and compliance daily for each patient, we used generalized linear mixed-effects models with the appropriate link function to estimate the mean and 95% CI for each parameter of interest. The model included a random intercept for patient, and ventilator protocol was the only fixed effect included. An *F* test for protocol effect was conducted for each model, followed by Tukey adjusted pairwise comparisons when necessary.

RESULTS

Patients

We enrolled a total of 52 patients in four participating ICUs with *n* equal to 17, 18, and 17 in the VC-LTV, APRV-LTV, and APRV arms, respectively (Fig. 1). In the mixed surgical, trauma, and medical study ICUs, the majority of patients who were screened for eligibility did not meet the inclusion criteria (Fig. 1). There was no difference in Pao_2/Fio_2 ratio between the groups before randomization or at the time of protocol initiation (VC-LTV = 131, APRV-LTV = 98, APRV = 106; $p = 0.78$) (**Table 1**). Baseline demographics did not differ significantly across the three arms (Table 1).

Clinical Outcomes

In-hospital mortality for the cohort was 40% (21/52) with no significant difference among the arms ($p = 0.20$). We found

TABLE 1. Demographic and Baseline Information

Demographic Characteristic	LTV-Volume Control *n* = 17	APRV-LTV *n* = 18	APRV *n* = 17	*p*
Demographics, reported as mean (SD) or *n* (%)				
Age	51 (14)	57 (14)	57 (16)	0.42
Female sex	9 (53)	9 (50)	5 (29)	0.37
Acute Physiology and Chronic Health Evaluation II	32 (10)	27 (7)	28 (9)	0.19
Cause of respiratory failure, *n* (%)				0.51
Sepsis	5 (29)	5 (28)	3 (18)	
Pneumonia	5 (29)	4 (22)	7 (41)	
Aspiration	0 (0)	3 (17)	1 (6)	
Trauma	1 (6)	0 (0)	3 (18)	
Cardiac arrest	2 (12)	1 (5)	1 (6)	
Other (medical/surgical)	4 (24)	5 (28)	2 (12)	
Vasopressors at the time of randomization, reported as median (IQR) or *n* (%)				
Requiring vasopressors	9 (53)	9 (50)	5 (29)	0.37
Norepinephrine equivalent dose[a] (μg/kg/min)	0.07 (0.03–0.65)	0.10 (0.06–0.12)	0.11 (0.04–0.17)	0.92
Baseline ventilator parameters, reported as median (IQR)				
Set V_T/kg (at baseline)	6.0 (5.9–6.4)	6.1 (6.0–6.5)	6.1 (6.0–6.6)	0.61
Measured V_T/kg (final vent check before randomization)	6.2 (6.0–6.5)	6.1 (6.0–6.5)	6.1 (6.0–6.6)	0.96
Pao_2/Fio_2 ratio (final vent check before randomization)	131 (85–147)	98 (73–156)	106 (80–159)	0.78

APRV = airway pressure release ventilation, IQR = interquartile range, LTV = low tidal volume, V_T = tidal volume.
[a]Among patients requiring vasopressors at randomization.

no difference in day 3 Pao_2/Fio_2 ratio, barotrauma, ICU LOS, hospital LOS, VFDs, or reintubation rate among the arms (**Table 2**); this persisted after linear regression adjusted for severity of illness.

Ventilator Parameters

Figure 2 depicts the average daily measured V_T by patient for each protocol arm. Thirty-five percent of APRV and 17% of APRV-LTV patients had at least one study day with average measured release volume greater than 12 mL/kg (Fig. 2). Patients in the VC-LTV arm had significantly lower average daily V_Ts with less variability than those in either APRV arm (VC = 6.8 mL/kg [6.2–7.5 mL/kg], APRV-LTV = 8.0 mL/kg [7.3–8.9 mL/kg], APRV = 8.6 mL/kg [7.8–9.6 mL/kg]; $p = 0.005$).

We found no significant difference between P_{aw} (VC-LTV = 13.6, APRV-LTV = 15.7, APRV = 16.1; $p = 0.15$) between arms, but higher PIP in the conventional arm (VC-LTV = 23.9, APRV-LTV = 20.2, APRV = 19.5; $p = 0.03$) (Table 2). The lowest daily MAP and highest daily CVP were also similar. Average daily compliance for each protocol was similar ($p = 0.61$) and ranged between 91% and 95% (Table 2). Mean and SDs of ventilator parameters through study day 5 is presented in **Table 3**.

Medication Administration

The proportion of patient days on which patients received vasoactive medication was 59% in the VC-LTV arm compared with 10% and 21% in the APRV arms ($p = 0.20$). We observed no significant difference in the rate of benzodiazepine receipt among the arms (VC-LTV = 9%, APRV-LTV = 8%, APRV = 18%; $p = 0.42$). Similarly, there was no statistical difference in the total dosage of dexmedetomidine (VC-LTV = 17.4 mg/kg/d, APRV-LTV = 15.4 mg/kg/d, APRV = 21.6 mg/kg/d; $p = 0.66$) or propofol medication (VC = 26.1 µg/kg/d, APRV-LTV = 26.1 µg/kg/d, APRV = 37.1 µg/kg/d; $p = 0.17$). The rate of administration of paralytics, opioids, and typical or atypical antipsychotics was also similar (Table 2).

DISCUSSION

This is the first multicenter randomized controlled trial (RCT) of an LTV ventilation APRV protocol tracking release volumes in patients with hypoxemic respiratory failure. We observed no difference in oxygenation on day 3 of mechanical ventilation between VC-LTV and APRV, although the study was underpowered. Similarly, we observed no difference in sedation requirements, VFDs, or hospital mortality among the protocols. We importantly demonstrate that in four ICUs with years of ventilator protocol experience, neither the APRV-LTV nor the standard APRV protocol was associated with adherence to a LTV (6 mL/kg) ventilation target; that both APRV protocols resulted in variable release volumes with many greater than 12 mL/kg. Despite high daily compliance, our APRV-LTV protocol was unable to achieve LTV targets. Given the evidence in support of LTV ventilation, we propose that in the absence of a protocol that demonstrates successful achievement of LTV with APRV, the use of APRV should be limited to controlled clinical trials (8, 28).

The mortality benefits of APRV remain unproven. APRV appears to improve oxygenation or Pao_2/Fio_2 ratio in patients with hypoxemic respiratory failure (5, 16, 32–42). Although clinicians often titrate mechanical ventilation to optimize oxygenation, LTV is what confers mortality benefit, not improvement in oxygenation (1). Furthermore, clinicians titrate APRV with different application, making comparisons of published prospective studies difficult (18, 39, 42–44), and making a reproducible APRV protocol challenging. The single-center study by Zhou et al (42) favors APRV over LTV but may be contingent on the individual titration of APRV for each patient. Animal data and one observational study suggest that early application of APRV may reduce the occurrence of ARDS (33, 39, 40, 45–48). However, higher quality evidence indicates that LTV ventilation may be a better strategy more consistently applied for ARDS prevention (7, 8, 10–12, 49–51). Our study results do not suggest that APRV will improve patient comfort or reduce mortality and are supported by Lalgudi Ganesan et al (52) who found no difference in sedation and increased mortality with APRV. They suggest that a higher spontaneous-to-mandatory breath ratio observed in the APRV group could portend harm (52). Because of increased release volumes observed with APRV in our study, APRV may be inferior to VC-LTV ventilation. Although the harms of large release volumes in humans are yet unproven, animal studies demonstrate greater alveolar microstrain and decreased dynamic alveolar homogeneity with larger release volumes (47, 53). We assert that until implementation of APRV successfully adheres to LTV ventilation or can be tested in a reproducible manner across several centers, APRV compares unfavorably with LTV ventilation for prevention or treatment of ARDS (8, 11, 52). We express concern that although a multicenter study of APRV is justified, it may not be feasible using current protocols.

Prospective evaluations of the efficacy of APRV in patients are limited (13, 26, 54, 55). Our study is the second RCT comparing APRV to VC-LTV ventilation in a mixed population with acute hypoxemic respiratory failure, and the first prospective trial of an explicit APRV-LTV protocol. Maxwell et al (54) found no difference in clinical outcomes between APRV and VC-LTV in trauma patients. The single-center study by Zhou et al (42) reported an increase in VFDs and reduced sedation requirements with traditional APRV. The findings by Zhou et al (42) may be linked to key design elements as sedation and VFDs are linked; respiratory therapists manipulated APRV settings per subject and changed sedation medication to achieve spontaneous breath goals that may have introduced treatment bias (42). The individualized treatment by Zhou et al (42) of each APRV patient also raises concerns about the feasibility of reproducing the trial in other centers. Our study used explicit reproducible ventilator protocols (Supplement B, Supplemental Digital Content 2, http://links.lww.com/CCM/E40) that were managed by the respiratory therapists and titration of sedation was managed independent of the ventilator by the bedside nurses. Our observations

TABLE 2. On-Study Ventilatory Parameters, Protocol Compliance, and Outcomes

Study Outcome	LTV-Volume Control *n* = 17	APRV-LTV *n* = 18	APRV *n* = 17	*p*
On-study ventilatory parameters,[a] reported as mean estimate (95% CI) from a mixed-effects model				
Average daily tidal volume/kg[b]				
Measured/release	6.8 (6.2–7.5)	8.0 (7.3–8.9)	8.6 (7.8–9.6)	**0.005**
Spontaneous	Not available	6.1 (5.2–7.2)	5.3 (4.5–6.3)	0.25
Mean airway pressure	13.6 (11.8–15.4)	15.7 (13.9–17.6)	16.1 (14.2–18.1)	0.15
Peak inspiratory pressure/daily peak high positive end-expiratory pressure	23.9 (21.6–26.3)	20.2 (17.7–22.8)	19.5 (16.9–22.2)	**0.03**
On-study hemodynamics, reported as mean estimate (95% CI) from a mixed-effects model				
Lowest daily mean arterial pressure	59 (54–63)	64 (60–69)	66 (62–71)	0.07
Highest daily central venous pressure	14 (12–16)	13 (11–15)	12 (10–15)	0.44
Protocol compliance, reported as median (IQR) or mean estimate (95% CI) from a mixed-effects model				
Days on study	7 (3–12)	3 (2–4)	3 (2–4)	**0.018**
Rate of protocol compliance[c]	92 (82–96)	91 (78–96)	95 (85–99)	0.61
Medication administration, reported as mean estimate (95% CI) from a mixed-effects model				
Frequency of medication administration (%)				
Vasopressors	59 (17–91)	21 (3–67)	10 (1–52)	0.20
Narcotics	68 (38–88)	51 (23–79)	69 (37–90)	0.68
Benzodiazepines	9 (4–21)	9 (3–21)	18 (7–37)	0.42
Paralytics	13 (7–22)	13 (6–24)	11 (5–22)	0.91
Sedation (continuous infusion)	64 (38–84)	70 (42–88)	53 (26–79)	0.71
Medication dosage				
Norepinephrine equivalent–weighted mean dose (μg/kg/min)	0.14 (0.08–0.25)	0.12 (0.06–0.23)	0.06 (0.03–0.14)	0.30
Propofol dose (mg/kg/d)	26.1 (18.2–34.0)	26.1 (17.8–34.3)	37.1 (27.9–46.4)	0.17
Dexmedetomidine dose (μg/kg/d)	17.4 (12.3–22.5)	15.4 (8.2–22.5)	21.6 (10.7–32.5)	0.66
Outcomes, reported as median (IQR) or *n* (%)				
Day 3 P/F ratio[d]	161 (142–184)	165 (115–236)	165 (134–209)	0.92
Hospital mortality	10 (59)	6 (33)	5 (29)	0.20
Barotrauma	1 (6)	0 (0)	0 (0)	0.65
Reintubation	3 (18)	4 (22)	0 (0)	0.10
Ventilator-free days to day 28[e]	0 (0–18)	22 (0–24)	20 (0–24)	0.10
ICU LOS (d)	8.2 (4.7–18.6)	5.8 (4.0–9.6)	8.7 (5.9–14.0)	0.47
Hospital LOS (d)	8.3 (7.2–18.8)	9.2 (5.0–13.4)	11.9 (9.7–17.9)	0.26

APRV = airway pressure release ventilation, IQR = interquartile range, LOS = length of stay, LTV = low tidal volume.

[a]These omit study days on continuous positive airway pressure (CPAP) and pressure support. We included a patient day if they were on LTV-volume control (VC), APRV-LTV, or APRV for at least 1 hr that day and reported tidal volume information for only while they were on LTV-VC, APRV-LTV, or APRV.

[b]Average daily tidal volume (V_T)/kg is the average of all V_T/kg available while on protocol ventilation on a given day.

[c]These percentages are based only on study days where the patient was on one of the study ventilation modes. If a patient was only on CPAP or pressure support for a calendar day, that day was not assessed for compliance.

[d]This analysis is limited to patients who survive to day 3 (*n* = 47; of the 5 who died by day 3, 2 were on LTV-VC, 1 was on APRV-LTV, and 2 were on APRV). This is the Pao_2/Fio_2 (P/F) ratio closest to 8 AM on the study day 3 where the following prioritization was used: 1) P/F ratio based on an arterial blood gas (ABG) within 2 hr of 8 AM; 2) P/F ratio imputed from an peripheral capillary oxygen saturation (Spo_2) and Fio_2 obtained within 2 hr of 8 AM; 3) P/F ratio based on an ABG closest to 8 AM on study 3; and 4) P/F ratio imputed from an Spo_2 and Fio_2 obtained within 2 hr of 8 AM; 3) P/F ratio based on an ABG closest to 8 AM on study 3; and 4) P/F ratio imputed from an Spo_2 and Fio_2 obtained closest to 8 AM on study day 3.

[e]If the patient died before day 28, their ventilator-free days were set to 0.

Boldface values are statistically significant values.

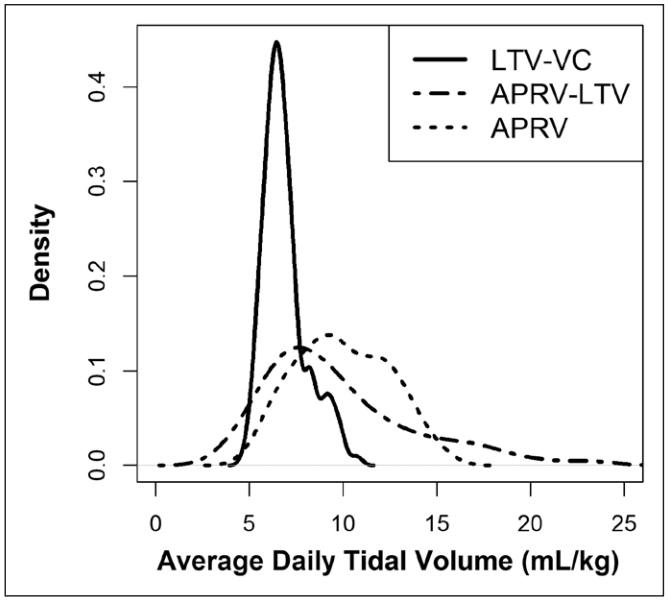

Figure 2. Density plot of the distribution of average daily tidal volumes by protocol. APRV = airway pressure release ventilation, LTV = low tidal volume, VC = volume control.

do not support previously noted reduced sedation requirements with APRV (25, 26).

Spontaneous breathing during APRV occurs any time during the ventilator cycle and is recorded as tidal breathing. The two-way valve on the Draeger EvitaXL allows for the patient to inhale or exhale during P_{low}, P_{high}, or during the release phase. The majority of time during the ventilator cycle in APRV is spent at P_{high}; therefore, tidal breathing occurs largely at P_{high} and generates pressures above P_{high}. Many APRV protocols add tube compensation to the spontaneous efforts which enhances tidal efforts similar to pressure support. Release breaths serve to augment ventilation and are titrated (28, 56, 57). A tidal breath occurring at the end of P_{high} allows the patient to augment the release breath with exhalation of their tidal breath. Similarly, spontaneous inspiration during the ascending phase of the release breath allows the patient to inhale additional volume above that required to reach P_{high}. Duration of the release breath is short, meant to prevent alveolar collapse and is determined by the time spent at P_{low} (14, 58). Release volume is quickly returned, is rarely tracked, yet represents the volume required to reestablish P_{high}. Alveoli can collapse very quickly, and the main determinant of how much collapse occurs is the volume that leaves the lungs during P_{low}. We submit that the release breath, not the spontaneous efforts in APRV, represents the volume change experienced in the alveoli. Neither Zhou et al (42) nor Maxwell et al (54) report measured release volumes. Our findings highlight the variability in measured release and spontaneous breaths during APRV ventilation (Fig. 2 and Table 2).

Inconsistent V_Ts with corresponding increases in transalveolar pressure may confer risk of VILI during spontaneous efforts in mechanically ventilated patients and such variability is common in APRV (38, 52, 57, 59–62). Increased driving pressure and transalveolar pressures may be more directly related to VILI (60, 61). In our findings, 35% of APRV and 17% of APRV-LTV patients had at least one study day where the average measured release volume was greater than 12 mL/kg (Fig. 2) which supports concerns about potential harms (28, 61, 63). The P_{aw} in APRV is often considered to be similar to the intrinsic PEEP required by the patient to achieve the

TABLE 3. Ventilator Parameters Across the Study Period

Study Day	LTV-Volume Control	APRV-LTV	APRV
Measured/release V_T/kg, mean (SD) (sample size for group and time point)			
Prerandomization[a]	7.0 (2.7) (17)	6.2 (0.6) (18)	6.4 (0.7) (17)
Day 1	7.0 (1.3) (17)	8.3 (2.2) (17)	8.6 (1.8) (15)
Day 3	6.9 (1.4) (11)	9.1 (2.8) (6)	10.6 (2.8) (6)
Day 5	6.9 (1.1) (10)	15.5 (1.5) (2)	10.4 (1.4) (2)
Spontaneous V_T/kg,[b] mean (SD)			
Prerandomization	NA	NA	NA
Day 1	NA	6.2 (1.5)	6.2 (2.4)
Day 3	NA	6.9 (1.9)	6.1 (1.9)
Day 5	NA	9.2 (0.8)	7.3 (1.9)
Mean airway pressure, mean (SD)			
Prerandomization	15 (6)	14 (4)	14 (4)
Day 1	14 (5)	16 (5)	15 (6)
Day 3	14 (3)	15 (7)	16 (5)
Day 5	15 (3)	20 (8)	24 (3)
Peak inspiratory pressure/daily peak high PEEP, mean (SD)			
Prerandomization	26 (8)	24 (7)	25 (7)
Day 1	25 (9)	22 (6)	18 (7)
Day 3	24 (8)	19 (9)	18 (5)
Day 5	25 (5)	27 (12)	27 (6)
$PEEP_T$[c] mean (SD)			
Prerandomization	9 (5)	11 (4)	10 (4)
Day 1	10 (4)	8 (5)	3 (2)
Day 3	9 (4)	8 (5)	4 (2)
Day 5	10 (3)	8 (1)	6 (0)

APRV = airway pressure release ventilation, LTV = low tidal volume, NA = not applicable, PEEP = positive end-expiratory pressure, V_T = tidal volume.

[a]Prerandomization summarizes the values from the vent check just before randomization.

[b]Spontaneous V_T/kg is only reported for the APRV arms on days 1, 3, and 5 because the majority of patients were on pressure regulated volume control before randomization.

[c]PEEP is measured at the end of $time_{low}$ in APRV.

critical opening pressure on the hysteresis curve but often it approaches P_{high} (28, 64, 65). In our study, both APRV protocols demonstrated numerically higher P_{aw} compared with VC-LTV. Spontaneous breaths at higher P_{aw} may result in even higher transalveolar pressures with unknown risks (28, 37, 61, 63, 64). Additional clinical studies measuring transalveolar pressure during release breaths and spontaneous efforts on APRV are warranted.

This study has several limitations. Clinicians were not blinded to the treatment arm. Although our study is comparable in size to other APRV trials (52, 54), we did not reach our target enrollment. Our study is thus underpowered, and negative findings of this trial may represent type 2 statistical error. The study was originally designed to evaluate oxygenation but was stopped prematurely due to inability to achieve LTV in APRV. Our patient enrollment was also smaller than enrollment in the trial by Zhou et al (42). However, our study cohort and mortality rate (consistent with severe to moderate ARDS) are representative of the population that currently triggers the clinical use of APRV (66). Our study protocol did not include an explicit sedation, pain management, or vasoactive medication protocol. Titration of sedation and pain control were performed by bedside clinicians using standard goal-directed delirium (Confusion Assessment Method for the ICU) and sedations assessments (Richmond Agitation-Sedation Scale). Similarly, vasoactive medications were titrated to goal MAP determined by the clinical team. It is possible that patients in the APRV arms were inappropriately perceived as more agitated or uncomfortable. Our data, however, are likely to mimic clinical application of sedation management with score-targeted sedation guidelines. Our findings may be specific to our protocol. It is unclear why titration of P_{low} and P_{high} did not result in targeted release breath values or if a different APRV-LTV protocol can achieve an average V_T less than 6.5 mL/kg. Although daily compliance was high, we used a paper protocol without assessment of compliance to each individual instruction. It is possible that an electronic APRV protocol would have tracked compliance more accurately and identified areas where the APRV-LTV protocol could have been changed to better achieve LTV targets.

CONCLUSIONS

An APRV-LTV protocol was implemented with adequate protocol compliance and resulted in highly variable release volumes that do not consistently achieve an LTV target (< 6.5 mL/kg). Average daily release volumes often exceeded 12 mL/kg. Our APRV-LTV protocol designed to limit release volumes was not feasible. Current APRV protocols are unable to achieve consistent and reproducible delivery of LTV ventilation goals. A large- scale efficacy trial of APRV-LTV is not feasible in the absence of a reproducible and easily generalizable APRV-LTV protocol.

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