Use of Airway Pressure Release Ventilation in Patients With Acute Respiratory Failure Due to COVID-19: Results of a Single-Center Randomized Controlled Trial*

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OBJECTIVES: Airway pressure release ventilation is a ventilatory mode characterized by a mandatory inverse inspiratory:expiratory ratio with a very short expiratory phase, aimed to avoid derecruitment and allow spontaneous breathing. Recent basic and clinical evidence suggests that this mode could be associated with improved outcomes in patients with acute respiratory distress syndrome. The aim of this study was to compare the outcomes between airway pressure release ventilation and traditional ventilation targeting low tidal volume, in patients with severe coronavirus disease 2019.

DESIGN: Single-center randomized controlled trial.

SETTING: ICU of a Mexican referral center dedicated to care of patients with confirmed diagnosis of coronavirus disease 2019.

PATIENTS: Ninety adult intubated patients with acute respiratory distress syndrome associated with severe coronavirus disease 2019.

INTERVENTIONS: Within 48 hours after intubation, patients were randomized to either receive ventilatory management with airway pressure release ventilation or continue low tidal volume ventilation.

MEASUREMENTS AND MAIN RESULTS: Forty-five patients in airway pressure release ventilation group and 45 in the low tidal volume group were included. Ventilator-free days were 3.7 (0–15) and 5.2 (0–19) in the airway pressure release ventilation and low tidal volume groups, respectively ($p = 0.28$). During the first 7 days, patients in airway pressure release ventilation had a higher Pao_2/Fio_2 (mean difference, 26 [95%CI, 13–38]; $p < 0.001$) and static compliance (mean difference, 3.7 mL/cm H_2O [95% CI, 0.2–7.2]; $p = 0.03$), higher mean airway pressure (mean difference, 3.1 cm H_2O [95% CI, 2.1–4.1]; $p < 0.001$), and higher tidal volume (mean difference, 0.76 mL/kg/predicted body weight [95% CI, 0.5–1.0]; $p < 0.001$). More patients in airway pressure release ventilation had transient severe hypercapnia, defined as an elevation of Pco_2 at greater than or equal to 55 along with a pH less than 7.15 (42% vs 15%; $p = 0.009$); other outcomes were similar. Overall mortality was 69%, with no difference between the groups (78% in airway pressure release ventilation vs 60% in low tidal volume; $p = 0.07$).

CONCLUSIONS: In conclusion, when compared with low tidal volume, airway pressure release ventilation was not associated with more ventilator-free days or improvement in other relevant outcomes in patients with severe coronavirus disease 2019.

KEY WORDS: acute respiratory distress syndrome; airway pressure release ventilation; coronavirus disease 2019; low tidal volume ventilation

The mortality in mechanically ventilated patients with severe acute respiratory failure due to novel coronavirus disease 2019 (COVID-19) is overwhelmingly high in some developing countries despite increasing adoption of protective lung ventilation and prone positioning (1). Over the pandemic, controversy arose on the best way to manage mechanical ventilation (2). Although an overabundance of information saturated the literature (3), we still lack randomized controlled data that can yield information on what strategy to use.

A recent randomized controlled trial (RCT) comparing airway pressure release ventilation (APRV) with low tidal volume (LTV) ventilation in non-COVID-19 patients with acute respiratory distress syndrome (ARDS) showed a significant reduction in sedation requirement, ventilator days, ICU stay, and tracheostomy (4). However, the study had significant limitations, as patients in control group had more comorbidities, pneumonia as the cause of the ARDS, higher incidence of vasopressor support, and sedation management was different (5).

Our center has an ongoing RCT comparing early application of APRV with LTV in patients with ARDS. Our hypothesis was that APRV, by allowing spontaneous ventilation and less use of sedation, would improve outcomes. The COVID-19 pandemic rapidly increased enrollment of patients into our trial. After four cases of barotrauma developed in a short time frame, a nonprespecified interim analysis was performed, which led to recommendations to modify trial enrollment. We present the analysis of 90 patients with COVID-19 that were enrolled in the trial.

MATERIALS AND METHODS

This is an analysis of patients with reverse transcriptase-polymerase chain reaction–confirmed COVID-19 enrolled in an RCT comparing APRV with LTV ventilation in patients with early ARDS (ClinicalTrials.gov: NCT04221737). COVID-19 patients were enrolled from March 1, 2020, to November 30, 2020. Patients were randomized to either APRV or LTV within 48 hours of endotracheal intubation. After randomization, all patients received a 12-hour stabilization period of protective LTV ventilation. Patients on the LTV group continued on mechanical ventilation according to the ARDS Network protocol (6), with a tidal volume (V_T) of 6 mL/kg of predicted body weight (PBW), with

lower limit to 4 mL/kg/PBW in the case of plateau pressure greater than 30 cm H_2O and upper limit to 8 mL/kg/PBW if needed to manage patient-ventilator interactions or acidosis. Patients on the intervention group were managed with APRV. Briefly, initial settings on APRV were as follows: high pressure (inspiratory pressure [P-high]) was set at the same Pplat measured on an inspiratory pause of 0.5 seconds in previous volume-controlled mode, with a maximum allowed level of 30 cm H_2O; low pressure was set always at 0 cm H_2O; inspiratory time (T-high) was initiated at 4 seconds; and expiratory time (T-low) was set at 0.4–0.6 seconds, but immediately adjusted upon analysis of flow-time curve at expiration. The expiratory flow termination (E_{FT}) was maintained between 50% and 75% (of the peak flow), with preference to 75% (7), as supported by experimental (8) and observational clinical data from a center with long-standing experience (9). Other supportive therapies as analgesia, sedation, neuromuscular blocking, prone positioning, and mechanical ventilation weaning were standardized for both groups as defined by the research protocol (**Supplemental Digital Content 1, Protocol**, http://links.lww.com/CCM/G712). Data on ventilatory settings, blood gas analysis, and supportive therapies were recorded at 0, 3, 5, and 7 days after randomization, and patients were followed up for death or hospital discharge at 28 days. The primary outcome was ventilator-free days (VFDs) at 28 d, calculated as 28 − x if alive and successfully liberated from ventilation x days after initiation, and defined as 0 if patient died within 28 days (10). Secondary outcomes included rate of severe hypercapnia (defined as an elevation of PCO_2 at ≥ 55 along with a pH < 7.15), recruitment maneuvers, barotrauma, tracheostomy rate, length of ICU stay, and all-cause hospital mortality.

The trial was designed considering a mean of 14 VFD (±8) in patients with moderate/severe ARDS at our center and a difference of 4 days as clinically important. Based on this, we calculated a sample size of 65 patients in each group, with 80% power and a two-sided–type error rate of 0.05.

Categorical variables are presented as numbers and percentages, and comparison between groups was performed with the chi-square or Fisher exact test as appropriate. Continuous variables are summarized as means ± sd if normally distributed or medians (25–75th) if nonnormally distributed, and were compared using Student t or Mann-Whitney U

test, respectively. For variables measured at multiple time points, repeated measures analysis of variance test was used. The comparison for cumulative survival at 28 days was performed with Kaplan-Meier analysis and log-rank test. All tests were two-tailed, and a *p* value of less than 0.05 was considered as significant. Statistical analysis and graphics were performed with GraphPad Prism Version 9.1.0 (GraphPad Software, San Diego, CA).

This study was performed in line with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal decision makers. Approval was granted by the Institutional Review Board at Hospital Civil Fray Antonio Alcalde (HCG/CEI-0632/17, 133/17).

RESULTS

During the study period, we enrolled 90 patients with ARDS due to COVID-19. Forty-five patients were randomized to APRV and 45 patients to continue on LTV (**Fig. 1**). All patients had moderate/severe ARDS (mean Pao_2/Fio_2, 144 ± 44) and were randomized within 16 hours (11–16) after intubation. There were no differences between the groups in baseline characteristics (**Table 1**). Regarding primary outcome, VFDs were 3.7 (0–15) and 5.2 (0–19) in the APRV and LTV groups, respectively ($p = 0.28$) (**Table 2**). During the first 7 days, patients on APRV had a higher Pao_2/Fio_2 (mean difference, 26 [95% CI, 13–38]; $p < 0.001$) and static compliance (mean difference, 3.7 mL/cm H_2O
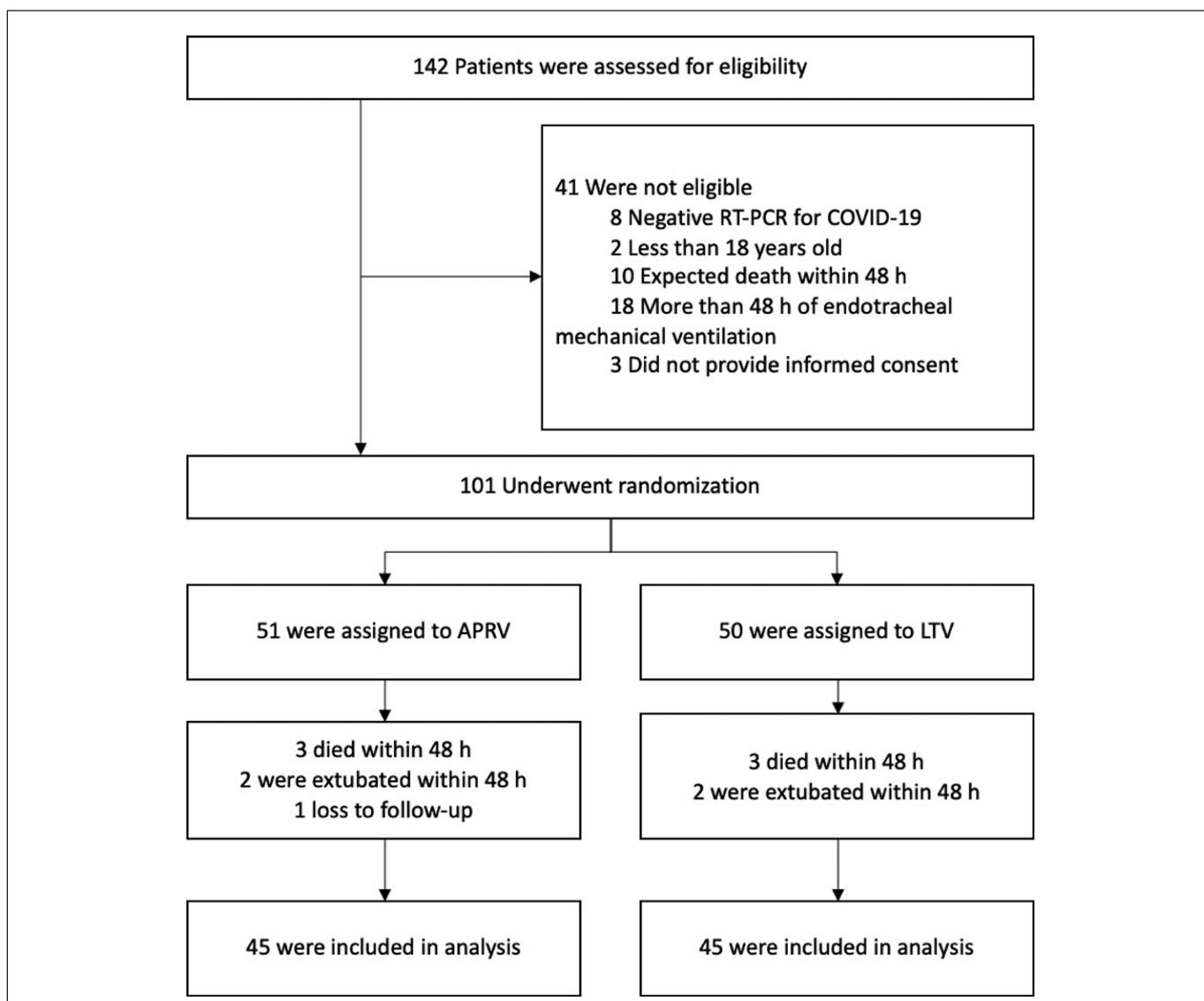

Figure 1. Flowchart of participants. APRV = airway pressure release ventilation, COVID-19 = coronavirus disease 2019, LTV = low tidal volume, RT-PCR = reverse transcriptase-polymerase chain reaction.

TABLE 1.
Baseline Characteristics

Characteristics	All (n = 90)	Airway Pressure Release Ventilation (n = 45)	Low Tidal Volume (n = 45)	p
Age	56 ± 15	55 ± 14.6	57 ± 15.4	0.66
Male, n (%)	63 (70)	32 (71)	31 (69)	0.81
Diabetes, n (%)	50 (55.6)	23 (51)	27 (60)	0.39
Hypertension, n (%)	44 (49)	20 (44)	24 (53)	0.40
Acute kidney injury, n (%)	47 (52)	21 (47)	26 (58)	0.29
Days of symptoms before intubation	9 (6–13)	8 (6–12)	10 (7–13)	0.20[a]
Use of high-flow nasal cannula, n (%)	44 (49)	20 (44)	24 (53)	0.40
Duration of high-flow nasal cannula (h)	22 (19–29)	19.5 (18–29)	23.5 (20.5–29.5)	0.15
Use of noninvasive ventilation before intubation, n (%)	11 (12.2)	5 (11.1)	6 (13.3)	0.74[b]
Duration of noninvasive ventilation before intubation (h)	10.4 ± 3.2	10.6 ± 1.8	10.3 ± 4.2	0.90
Intubation to randomization (h)	16 (13–18)	16 (14–18)	16 (13–19)	0.60[a]
Vasopressor requirement at randomization, n (%)	56 (62)	25 (55)	31 (68)	0.19
Norepinephrine dose (μg/kg/min)	0.10 (0.05–0.13)	0.08 (0.05–0.12)	0.11 (0.05–0.15)	0.34[a]
d-dimer (mg/L)	3.3 (2.7–3.8)	3.5 (2.8–3.8)	3.1 (2.7–3.5)	0.11[a]
Acute Physiology and Chronic Health Evaluation II score	14.8 ± 4.8	14.3 ± 4.7	15.3 ± 5.0	0.35
Tidal volume (mL/kg/predicted body weight)	6.5 ± 0.8	6.6 ± 0.8	6.5 ± 0.8	0.31
Mean airway pressure (cm H_2O)	19 ± 2.8	20 ± 2.6	19 ± 2.8	0.06
Positive end-expiratory pressure (cm H_2O)	14 (12–16)	14 (14–16)	14 (12–16)	0.29[a]
Plateau pressure (cm H_2O)[c]	28 (26–29)	28 (26–29)	27 (26–29)	0.20[a]
Driving pressure (cm H_2O)	13.8 ± 4.2	13.7 ± 3.6	13.8 ± 4.7	0.88
Static compliance (mL/cm H_2O)	31 ± 9.4	30 ± 9.7	32 ± 9.2	0.46
Pao_2/Fio_2 ratio	144 ± 46	140 ± 42	149 ± 50	0.35

[a]Mann-Whitney was performed instead of t test.
[b]Fisher exact test was performed instead of χ^2.
[c]Measured at an inspiratory 0.5-s pause maneuver.

[95% CI, 0.2–7.2]; p = 0.03), higher mean airway pressure (mean difference, 3.1 cm H_2O [95% CI, 2.1–4.1]; p < 0.001), and higher V_T (mean difference, 0.76 mL/kg/PBW [95% CI, 0.5–1.0 mL/kg/PBW]; p < 0.001). There was no difference between the groups in driving pressure (mean difference, 0.02 cm H_2O [95% CI, –0.70 to 0.75 cm H_2O]; p = 0.94) or Pco_2 levels (mean difference, 0.15 mm Hg [95% CI, –2.7 to 3.0 mm Hg]; p = 0.91) (**Fig. 2**; and **Table S1**, http://links.lww.com/CCM/G713). Description of ventilator settings for patients on APRV is shown in **Table 3**.

More patients in APRV had episodes of severe hypercapnia (42% vs 15%; p = 0.009); however, all cases were transient (≤ 24h) and not associated with hemodynamic changes. Three patients on APRV and two on LTV were crossed over due to intractable hypoxemia; however, there was no sustained clinical improvement after change of ventilatory mode in any case. The incidence of barotrauma was equal between both groups. Requirements of neuromuscular blockade, prone positioning, sedation, analgesia, and other therapeutic measures were similar (**Table S2**,

TABLE 2.
Comparison of Outcomes Between Groups

Outcomes	All (*n* = 90)	Airway Pressure Release Ventilation (*n* = 45)	Low Tidal Volume (*n* = 45)	*p*
Ventilator-free days at 28 d	4.5 (0–6)	3.7 (0–15)	5.2 (0–19)	0.28
Days of mechanical ventilation	9.5 (7–15)	9 (6–14)	10 (8–15)	0.28
ICU length of stay (d)	11 (9–16)	9 (7–16)	12 (8–17)	0.17
Extubation, *n* (%)	33 (36.7)	13 (29)	20 (44)	0.12
Tracheostomy, *n* (%)	24 (27)	9 (20)	15 (33)	0.15
Barotrauma,[a] *n* (%)	8 (9)	4 (9)	4 (9)	1.0[b]
Severe hypercapnia,[c] *n* (%)	26 (29)	19 (42)	7 (15)	0.009
Deep venous thrombosis, *n* (%)	10 (11)	6 (13)	4 (9)	0.73[b]
Death at 28 d, *n* (%)	62 (69)	35 (78)	27 (60)	0.07
Cause of death, *n* (%)				
Refractory hypoxemia, *n* (%)	10 (16)	7 (20)	3 (11)	0.49[b]
Refractory septic shock, *n* (%)	52 (84)	28 (80)	24 (89)	

[a]No identifiable cause other than mechanical ventilation.
[b]Fisher exact test was performed instead of χ^2.
[c]P_{CO_2} elevation ≥ 55 mm Hg associated with pH < 7.15.

http://links.lww.com/CCM/G714). Overall mortality in the group was 69%, with a median time to death of 9 days [7–12] (11, 12); the main cause of death was refractory septic shock in 84%, with no difference between the groups ($p = 0.49$); there was no significant statistical difference between the groups in mortality (78% in APRV vs 60% in LTV; $p = 0.07$). At Kaplan-Meier analysis, we found a hazard ratio of 1.8 for death at 28 days ($p = 0.01$) (**Fig. S1**, http://links.lww.com/CCM/G715; legend: Kaplan-Meier analysis for survival at 28 d).

Four episodes of barotrauma occurring over a short time frame (3 wk), all in the APRV group, led to a review by the safety monitoring board. Due to the results of trend in mortality at the bivariate analysis, log-rank test, and the higher incidence of hypercapnia, the safety monitoring board could not reach a unanimous decision and recommended stopping recruitment for patients with COVID-19.

DISCUSSION

This is the first study comparing outcomes between APRV and LTV in patients with COVID-19. We did not find a difference in VFD, sedation or analgesia needs, or barotrauma. There were increased episodes of transient hypercapnia.

We suspect the higher incidence of transient hypercapnia was the result of patient and implementation factors. Patients with COVID-19 could be more prone to develop hypercapnia. Some patients with COVID-19 have features of increased dead space (11), which is thought to be secondary to microvascular thrombosis creating ventilation-perfusion mismatch. This seems to be associated with elevated D-dimer levels (12), which was found in our population (median d-dimer, 3.3 mg/L). In terms of implementation, our APRV protocol was based on a widely distributed unpublished protocol (13), yet our application may have been different. In the management of hypercapnia, the protocol indicates the clinicians should decrease T-high to achieve greater mandatory ventilation (higher mandatory respiratory rate) over prolonging the T-low (to achieve larger release volumes). However, the clinicians may choose either; others may favor allowing spontaneous breaths (SBs). This variability may have several reasons, one being that there is no published consensus statement on the use of APRV or a trial guiding this strategy. Its developers explain that a briefer T-high is required/favored when APRV is used
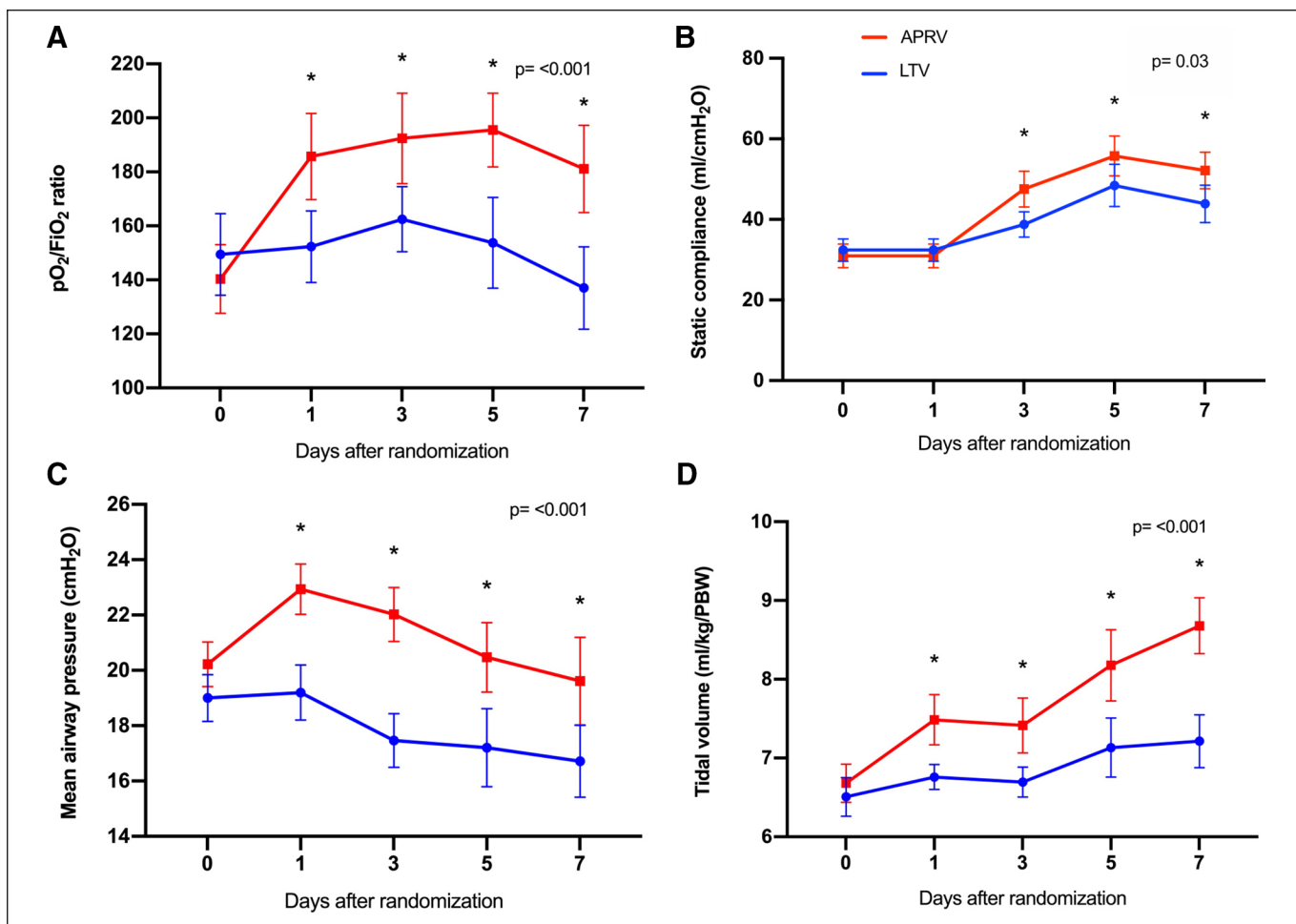
Figure 2. Ventilatory/oxygenation parameters at 0, 1, 3, 5, and 7 d after enrollment. **A**, Pao_2/Fio_2 ratio (mm Hg). **B**, Static compliance (mL/cm H_2O). **C**, Mean airway pressure (cm H_2O). **D**, Tidal volume (mL/kg/predicted body weight [PBW]). *p* values reported correspond to repeated measures analysis of variance test. *p value of less than 0.05 at bivariate analysis. APRV = airway pressure release ventilation, LTV = low tidal volume.

as a "rescue" strategy (other than postoperative atelectasis or normal lung) (13); therefore, it must be initially set to approximately match the rate on previous mode, which could frequently result in T-high less than or equal to 2 seconds. Our protocol had explicit recommendation to favor decreasing the T-high over the E_{FT}. However, based on our results, our clinicians were reluctant to use T-high lower than the typical 4–6 seconds. This may be the result of prior experience, practitioner favoring oxygenation goals, practice preference, or the lack of human clinical studies reporting use of such brief ranges. As an example, in a recent

TABLE 3.
Ventilator Settings in Airway Pressure Release Ventilation Group

Settings	Day 1	Day 3	Day 5	Day 7
Inspiratory pressure (cm H_2O)	26 (24–28)	26 (24–28)	24 (21–27)	22 (20–26)
Time of inspiratory pressure (s)	3.5 (3.0–3.6)	4.0 (4.0–4.5)	4.9 (4.5–5.5)	4.3 (4.0–4.6)
Time of expiratory pressure (s)	0.45 (0.40–0.55)	0.42 (0.40–0.45)	0.5 (0.45–0.55)	0.5 (0.45–0.55)
Expiratory flow termination (%)	68 ± 6.5	70 ± 6.2	63 ± 4.8	61 ± 3.6
Mandatory respiratory rate (beats/min)	15 (15–17)	13 (12–14)	11 (10–12)	13 (12–14)

Expiratory pressure was set at 0 cm H_2O in all patients, without adjustments.

survey including providers well-versed and with special interest in APRV, only 8% of responders considered a T-high of less than 4 seconds as adequate (14).

Before the initiation of the study, we performed a pilot phase with esophageal balloon measurements in eight patients with non-COVID-19 ARDS on APRV with SBs. We found transpulmonary pressure commonly exceeded 25 cm H_2O when P-high was set greater than 24 cm H_2O; therefore, we decided for safety reasons to allow SB only when P-high had decreased to less than or equal to 24 cm H_2O. This could have exposed patients to higher amount of sedatives/analgesia under our protocol (compared with other institution protocols). Interestingly, patients with COVID-19 seem to have a higher respiratory drive (15). COVID-19 may affect angiotensin-mediated sensitivity of the carotid bodies (which express angiotensin-converting enzyme 2 receptors) and disturb control of breathing (16). Although we did not measure esophageal pressure or other surrogates (i.e., P0.1 and change in airway pressure with an occlusion maneuver), a high respiratory drive may be inferred by the trend of progressive rise in V_T along with progressive decrease in mean airway pressure. SB during higher airway pressures can result in higher transalveolar pressures, a known cause of ventilator-induced lung injury, as it can potentially amplify the damage in severe lung injury (17, 18). There was no difference on the incidence of barotrauma; however, there was a higher nonstatistical trend to death from refractory hypoxemia on the APRV group. Therefore, we cannot rule out the development of ventilator-induced lung injury in patients of APRV group. APRV without SBs is inverse ratio ventilation, for which research was performed in the 1990s and mostly abandoned due to no major impact in outcomes (19, 20); yet, the differences with those ventilation strategies make it difficult to extrapolate. APRV allows unrestricted SBs throughout the respiratory cycle due to an active expiratory valve, the timing of the breath is set based on the expiratory flow (aiming to avoid derecruitment) rather than inspiratory:expiratory ratio, and the near-continuous elevated positive airway pressure (80–95% of the total cycle) (21), which is not specifically aimed even in recent inverse ratio ventilation studies (22). Overall, the challenge in mechanical ventilation with APRV is whether, in the sake of less sedation and paralysis, we should allow SB in patients with ARDS.

The APRV group had less patients achieving lung-protective V_T. This was consistent with the study by Hirshberg et al (23), who developed a protocol to compare volume-controlled ventilation with conventional APRV and a modified APRV designed to deliver LTV (LTV-APRV) in patients with non-COVID ARDS. In their study, the average VT during APRV was between 8 and 9 mL/kg/PBW, often exceeding 12 mL/kg/PBW. The recruitment was stopped early due to low enrollment and inability to achieve VT less than 6.5 mL/kg/PBW in the group of LTV-APRV. V_T while on APRV are not directly targeted but evolve directly related to the respiratory system characteristics (resistance, compliance, and patient effort). APRV is supposed to allow "personalization" of VT based on changes in lung physiology, in contrast to the prevailing "one size fits all" of 6 mL/kg/PBW (7). It has been suggested that APRV may prevent ARDS despite VT up to 12 mL/kg/PBW (24) and that could reduce microstrain and improve alveolar recruitment even with 11 mL/kg/PBW (8). Although perhaps possible in the laboratory, there is no practical way to achieve APRV with LTV at the bedside. The clinicians understanding of lung injury are deeply engrained in limiting volume, which may lead us to actions, in spite of a protocol, to achieve so. This is highlighted by the aforementioned survey study, in which only 8% of responders considered VT greater than 8 mL/kg/PBW as acceptable (14). If APRV does indeed protect the lung regardless of the VT, a study ensuring the clinicians can ignore VT is needed. This may be possible as more evidence is generated in lung protection based on driving pressure, power, and ARDS phenotypes (25), providing insight into how to better titrate delivery of mechanical ventilation.

Our results should be taken cautiously. The mortality in our study population was more than twice as reported in larger series of high-income countries (26); however, it mirrors the results of a recent nationwide report of 12,018 intubated patients with COVID-19 in Mexico (1). This is an ongoing single-center study designed to show difference in VFDs in non-COVID-19 patients; therefore, the study is underpowered to draw any conclusions on mortality (27). The main cause of death was septic shock, followed by refractory hypoxemia. It is possible that the mortality trends are independent of the mode of mechanical ventilation. Besides, we did not perform routine CT angiography for screening of pulmonary embolism, we

did not record the use of interleukin-6 modulators and adequacy of antibiotic administration according to the results of cultures, we have no details around timing of hypercapnia episodes, and the follow-up of measurements was limited to the first 7 days.

We are still learning the complex pathophysiology of COVID-19. The presence of endotheliopathy and excessive microthrombosis could also explain in part the lack of benefit of this open lung approach (28). The optimal ventilation strategy is still to be defined. However, emerging data from centers implementing LTV with lower mortalities (29, 30) support this strategy as the standard, whereas further data are generated on other optimal ventilation strategies.

CONCLUSIONS

APRV, when compared with LTV, was not associated with more VFDs or improvement in other relevant outcomes in patients with severe COVID-19; therefore, our data do not support its use as part of routine care in patients with severe COVID-19. Trials defining best implementation strategies, ideally with close monitoring of transpulmonary pressures, are needed.

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